CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022406Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 022406 SUPPL # N/A HFD # 160

Trade Name Xarelto

Generic Name rivaroxaban

Applicant Name Johnson and Johnson

Approval Date, If Known July 3, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Tyree Newman
Title: Regulatory Project Manager, DHP, OODP
Date: June 10, 2011

Name of Office/Division Director signing form: Ann Farrell
Title: Acting Division Director, DHP, OODP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TYREE L NEWMAN
06/15/2011

ANN T FARRELL
07/01/2011

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22406 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name:DHP PDUFA Goal Date: 7/3/2011 Stamp Date: 1/3/2011

Proprietary Name: Xarelto

Established/Generic Name: Rivaroxaban

Dosage Form: Tablet

Applicant/Sponsor: Johnson and Johnson Pharmaceutical Research & Development, LLC

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) N/A
(2) N/A
(3) N/A
(4) N/A

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing hip replacement surgery

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue

No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☒ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing knee replacement surgery

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☒ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☒ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☒ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

1.9.1 Request for Waiver of Pediatric Studies

The sponsor is requesting a waiver for the conduct of a clinical program with rivaroxaban for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in pediatric patients (<18 years of age) undergoing total hip or knee replacement surgery. The rationale for the waiver for the conduct of such a clinical program in this indication is the rarity of joint replacement surgery in the pediatric population and the lower risk of DVT and PE (collectively referred to as venous thromboembolism [VTE]), which does not necessarily require routine prophylaxis.

Patients over 40 years old have a clearly increased risk for the development of VTE across multiple clinical settings compared with younger patients. The incidence of VTE in children is considered rare and usually happens only in the presence of a strong predisposing risk factor (Anderson 2003). However, even with a strong predisposing factor like major trauma, the incidence of clinically-detected VTE is lower in patients 17 years old or less compared with those over 17 years, based on a Level 1 trauma center registry (Azu 2005). VTE events were experienced in:

- 0 of 2320 (0.0%) trauma patients under the age of 13 years
- 2 of 1025 (0.2%) trauma patients between the ages of 13 to 17 years
- 57 of 10549 (0.5%) trauma patients older than 17 years

Based on these data, the authors concluded that VTE prophylaxis after trauma is unnecessary in children since the risk of clinically significant VTE is negligible. In adults, routine VTE prophylaxis after major trauma is a Grade 1A recommendation (Geerts 2008). Similarly, a review of all patients 17 years old or less hospitalized for at least 72 hours and having 2 or more risk factors for VTE, found only 1 case with symptomatic DVT (Rohrer 1996). Since this patient had at least 3 risk factors for VTE (i.e., head trauma, neurologic deficit, and multiple surgeries), the authors conclude that VTE prophylaxis is not required for patients with only 1 or 2 risk factors.

Total joint replacements are performed in the pediatric population primarily for the joint deformities and disabilities associated with juvenile rheumatoid arthritis (and similar conditions) (Kim 2008, Kitsoulis 2006). Since these procedures are technically challenging and will eventually lead to revision surgery due to the finite functional lifespan of the artificial joint, they are performed infrequently and only after medical therapy has failed. Joint replacement surgery is also occasionally performed in pediatric patients for malignant bone disease (e.g., with proximal femoral resection) (van Kampen 2008). Reflecting the low number of surgeries, the largest case series reported in the literature has been 47 patients from the Mayo Clinic (Klassen 1979). There does not appear to be any data in the literature on the occurrence of VTE following joint replacement surgery in pediatric patients, but based on the above data in other settings, the VTE risk would be expected to be substantially lower than for adults.

Since pediatric subjects were excluded from all rivaroxaban clinical studies and the risk of VTE is likely different from that in adults, the safety and effectiveness of rivaroxaban have not been established in children and adolescents <18 years of age and therefore, rivaroxaban is not recommended for use in this population in the proposed product labeling.

The conduct of a clinical program to establish the safety and effectiveness of rivaroxaban in the pediatric population after joint replacement surgery is not feasible due to the limited number of procedures performed and the low expected incidence of symptomatic VTE events in this population. Therefore, the sponsor requests a waiver for the conduct of such a clinical program.

References

Anderson FA, Spencer FA. Risk factors for venous thromboembolism. Circulation 2003;107;I-9-I-16. 5.4-1

Azu MC, McCormack JE, Scriven RJ, Brebbia J, Shapiro MJ, Lee TK. Venous thromboembolic events in pediatric trauma patients: is prophylaxis necessary? J Trauma Inj Infect Crit Care 2005;59:1345-1349. 5.4-1

Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicans evidence-based clinical practice guidelines (8th edition). Chest 2008;133:381S-453S. 5.4-1

Kim HJ, Kahn B, Figgie MP. Total joint replacement in childhood arthritis. Curr Rheumatol Rep 2008;10(2):135-41. 5.4-1

Kitsoulis PB, Stafilas KS, Siamopoulou A, Soucacos PN, Xenakis TA. Total hip arthroplasty in children with juvenile chronic arthritis: long-term results. J Pediatr Orthop 2006;26(1):8-12. 5.4-1

Klassen RA, Parlasca RJ, Bainco AJ. Total joint arthroplasty. Applications in children and adolescents. Mayo Clin Proc 1979;54(9):579-82. 5.4-1

Rohrer MJ, Cutler BS, MacDougall E, Herrmann JB, Anderson FA, Wheeler HB. A prospective study of the incidence of deep venous thrombosis in hospitalized children. J Vascular Surg 1996;24(1)46-9. 5.4-1

van Kampen M, Grimer RJ, Carter SR, Tillman RM, Abudu A. Replacement of the hip in children with a tumor in the proximal part of the femur. J Bone Joint Surg (American) 2008;90(4):785-95. 5.4-1

Pediatric Research and Equity Act Waivers

NDA #:22-406 Supplement Type: N/A Supplement Number: N/A

Product name and active ingredient/dosage form: Xarelto (Rivaroxaban) Tablets

Sponsor: Johnson & Johnson

Indications(s): Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing hip replacement surgery
(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. Birth to age 16 years.

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

    a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

Indications(s): Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing knee replacement surgery
(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

3. Pediatric age group(s) to be waived. Birth to age 16 years.

4. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

    a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

Attachment I

Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver

These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis
Atherosclerotic cardiovascular disease
Benign prostatic hypertrophy
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders
Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:
- Basal cell
- Bladder
- Breast
- Cervical
- Colorectal
- Endometrial
- Gastric
- Hairy cell leukemia
- Lung (small & non-small cell)
- Multiple myeloma
- Oropharynx (squamous cell)
- Ovarian (non-germ cell)
- Pancreatic
- Prostate
- Renal cell
- Uterine

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/s/

MARCUS A CATO
06/06/2011

Newman, Tyree

From: Baugh, Denise
Sent: Thursday, June 30, 2011 5:42 PM
To: Newman, Tyree
Cc: Farrell, Ann T; Bridges, Todd
Subject: RE: NDA 22406 updated carton and containers (rivaroxaban)

Tyree, the revised label and labeling are acceptable.
Denise

-----Original Message-----
From: Newman, Tyree
Sent: Wednesday, June 29, 2011 9:29 PM
To: Baugh, Denise
Cc: Farrell, Ann T; Bridges, Todd
Subject: FW: NDA 22406 updated carton and containers (rivaroxaban)

Good evening Denise, please see the updated carton and container labels for your review.

Please inform me if the Sponsor addressed your requirements.

Kind regards,

Tyree

Mr. Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

-----Original Message-----
From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Wednesday, June 29, 2011 6:52 PM
To: Newman, Tyree
Subject: RE: NDA 22406 updated carton and containers (rivaroxaban)

Hi Tyree
Attached are the updated labels for the bottle, the carton and the HUD blister.
Best regards
Andrea

-----Original Message-----
From: Kollath, Andrea [PRDUS]
Sent: Wednesday, June 29, 2011 9:57 AM
To: Newman, Tyree
Subject: RE: NDA 22406 updated carton and containers for NDA 022406

Hi Tyree
Thanks. We will send as soon as the revisions have been made.
Andrea

-----Original Message-----
From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]
Sent: Wednesday, June 29, 2011 9:02 AM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 updated carton and containers for NDA 022406

Good morning Andrea, we have reviewed your updates to the carton and label containers and there are two issues which have not been satisfactorily addressed:

1) Increase the prominence of the established name by decreasing the font size/width of the proprietary name or increasing the font size/width of the established name such that they will be equally prominent.

2) Relocate the dosage form, 'tablets' to the left and relocate the strength, 10 mg to the right of it such that the dosage form and the strength appear on one line under the proprietary name.

Once you have made the updates, please send to my attention for review. If you have any additional questions, please let me know.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
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/s/

TYREE L NEWMAN
07/01/2011

Newman, Tyree

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, June 24, 2011 2:10 PM
To: Newman, Tyree
Subject: RE: NDA 22406 teleconference minutes
Attachments: emfinfo.txt

Thank you.

From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]
Sent: Friday, June 24, 2011 1:59 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 teleconference minutes

Good afternoon Andrea, per our teleconference yesterday regarding the Clinical Pharmacology section of the label for NDA 22406, I have summarized the meeting as follows:

The following attendees were present:

FDA Attendees (Agency):

- Joseph Grillo, Pharm.D.– Clinical Pharmacology Reviewer
- Julie Bullock, Pharm.D. – Clinical Pharmacology Team Leader
- Nitin Mehrotra – Pharmacometrics Reviewer
- Gabrielle Richterman, Pharm.D., student
- Tyree Newman – Regulatory Project Manager
- **Johnson and Johnson (Sponsor) attendees:**
- Gary Peters , MD, VP, Cardiovascular and Metabolism Clinical Development
- Paul Burton MD PhD FACC, VP Franchise Medical Leader
- Troy Sarich PhD, Compound Development Team Leader
- Kenneth Todd Moore, MS, Clinpharm Leader Rivaroxaban
- Judy Kinaszczuk, R.Ph. Director, Global Labeling
- Sanjay Jalota, MRPharmS, Regulatory Global Regulatory Lead
- Andrea Kollath, DVM, North America Regulatory Lead

Bayer Attendees (Sponsor):

- Scott D. Berkowitz, MD, VP, Global Clinical Dev. Head
- Dagmar Kubitza, MD PhD Global Clinical Pharmacology Project Leader, BSP
- Wolfgang M. Mueck, PhD. Director Clinical Pharmacokinetics
- Andrea Derix, PhD, Sen. Global Regulatory Strategist

The following is a summary of the primary discussion points between the Agency and the Sponsor:

- The Division clarified its rationale for including all the in vivo drug interaction information in Section 7 of the draft labeling rather than splitting between Sections 7 and 12. The Sponsor was concerned that there may be changes as they are working with Cardio-Renal Division on the label. The Division confirmed that Cardio-Renal has been involved in the current labeling review.
- The Division clarified its rationale for omitting PgP potency claims by stating that the Agency is not ready to endorse claims regarding PgP potency in labeling at this time.
- The Division provided clarification regarding its rationale for including Section 7.2 (Complex Drug-Disease Interactions) by stating simulations from both the sponsor and FDA reported the potential for a significant increase in rivaroxaban exposure that the team felt required further assessment as a PMR. Once the PMR has been completed and if the data suggests the label should be revised, the Sponsor can submit a supplement.
- The Division provided clarification regarding its rationale for removing (b) (4) throughout the draft labeling.
- The Division stated that the Sponsor is free to propose revised wording for the introductory paragraph for Section 7.1. However, the Division stressed the quantitative information regarding the extent of the interaction should remain in the noted list drugs in this section.
- The Division stated that the Sponsor may propose changes regarding the use of the term(s) "Avoid" or "Not recommended" or "Use with caution" as long as they are using “active voice".
- The Division stressed that the sponsor is free to submit proposed language for the draft labeling. These proposals would be carefully reviewed, but it should not be assumed they are acceptable to the Agency.
- The Division has completed the review of the label based on the data received in response to the CR. The Division will not be able to review any new data for this submission.

Please inform me if you have any questions or comments.

Kind regards,

Tyree

Tyree Newman

Regulatory Project Manager

Food and Drug Administration

Division of Hematology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

10903 New Hampshire Ave.

Silver Spring, MD 20993

301-796-3907 (phone)

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Tyree.Newman@fda.hhs.gov

APPEARS THIS WAY ON ORIGINAL

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/s/

TYREE L NEWMAN
06/30/2011

Newman, Tyree

From: Newman, Tyree
Sent: Wednesday, June 22, 2011 10:36 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 PMR

Good day Andrea, please see the final proposed post-marketing trial request from our review team regarding NDA 22406. Please review and respond by Friday, June 24, 2011. Pleas provide your proposed completion dates and we will confirm if we are in agreement with your proposal.

Post-marketing Requirements (PMR) for Rivaroxaban:
Under FDAAA, the FDA has determined that you are required to conduct the following:

A post-marketing study consisting of the mandatory collection and reporting of events of interest with enhanced pharmacovigilance (described below) to monitor, summarize, and report on risk factors, clinical management and outcome of cases of major bleeding in association with Rivaroxaban use post-marketing. (Major bleeding: must be defined noted in the clinical protocols and current drug labeling)

Submit a pharmacovigilance plan to describe how you will collect, follow-up, and analyze pertinent clinical information from all spontaneous, published literature, or solicited case reports of major bleeding.

In the protocol, describe:

The methods to be used for data collection and analysis, including your solicitation of reports of bleeding events
The plan for enhanced follow-up with reporters – You will actively query and ascertain key facts about the bleeding event, including:

- Demographics (age, gender, race, location of bleeding…….)
- Underlying diagnoses including specific reason for Rivaroxaban treatment
- Other relevant risk factors for bleeding
- Dose and duration of Rivaroxaban therapy
- Concomitant medications
- Treatment given for the bleeding (names of products, doses and duration of treatment)
- Any laboratory monitoring tests performed

Outcome information on:
- Bleeding outcome – time to cessation and opinion on the role of therapy given on the bleeding cessation
- Survival / disability / further complications

Submit summary information (total cases and summary of key facts in those cases, with pertinent expert analysis of clinically relevant information from the case series and any potential regulatory implications such as label changes) quarterly for 3 years then annually.

Provide expected completion dates
* Final Protocol Submission: _____
* Study Trial Completion: _____
* Final Report Submission: _____

If you have any questions, please let me know.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products

Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
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/s/

TYREE L NEWMAN
06/23/2011

Newman, Tyree

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Tuesday, June 21, 2011 2:40 PM
To: Newman, Tyree
Cc: Lu, Min; Robie Suh, Kathy M
Subject: RE: NDA 22406 teleconference
Attachments: emfalert.txt

Hi Tyree,
Thank you for the minutes. We appreciate the opportunity to discuss these topics. Just let us know when you have a time slot for the telecon for the next topic. Our team is on standby this whole week.
Best regards,
Andrea

From: Newman, Tyree [mailto:Tyree.Newman@fda.hhs.gov]
Sent: Tuesday, June 21, 2011 2:31 PM
To: Kollath, Andrea [PRDUS]
Cc: Lu, Min; Robie Suh, Kathy M
Subject: NDA 22406 teleconference

Good afternoon Andrea, per our teleconference this morning to discuss the issue of "Major bleeding" in Table 1 of the label for NDA 22406. The following attendees were present:

FDA Attendees (Agency):
- Dr. Min Lu - Clinical Reviewer
- Dr. Kathy Robie-Suh - Clinical Team Leader
- Tyree Newman - Regulatory Project Manager

Johnson and Johnson (Sponsor) attendees:
- Gary Peters , MD, VP, Cardiovascular and Metabolism Clinical Development
- Paul Burton MD PhD FACC, VP Franchise Medical Leader
- Leonard Oppenheimer, PhD. Statistical Sciences
- Juliana Ianus, Ph.D. Statistical Sciences
- Judy Kinaszczuk, R.Ph. Director, Global Labeling
- Sanjay Jalota, MRPharmS, Regulatory Global Regulatory Lead
- Andrea Kollath, DVM, North America Regulatory Lead

Bayer Attendees:
- Scott D. Berkowitz, MD, VP, Global Clinical Dev. Head,.
- Martin Homering PhD, Statistical Sciences

During the meeting, the following was agreed:

- Only "Major Bleeding" and "Any Bleeding" will be addressed in Table 1 of the label and "Any Bleeding" will be defined by the Sponsor in a foot note.
- The Agency will remove the comment, [redacted] (b) (4) from the label".

Action items

- The Sponsor requested a separate teleconference with the Clinical and Clinical Pharmacology reviewers to discuss concerns regarding comments noted in the label.
- The Sponsor requested a separate teleconference with DSI and the Clinical Reviewers to discuss data in

Records 1-4.

Please inform me if you have any questions or comments.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
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/s/

TYREE L NEWMAN
06/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Tyree Newman, RPM, Division of Hematology Products	
DATE June 16, 2011	IND NO. N/A	NDA NO. 22406	TYPE OF DOCUMENT PMR	DATE OF DOCUMENT N/A
NAME OF DRUG Xarelto (Rivaroxaban)	PRIORITY CONSIDERATION Rush		CLASSIFICATION OF DRUG Anticoagulant	DESIRED COMPLETION DATE June 20, 2011

NAME OF FIRM: Johnson and Johnson

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
We in DHP think we will want a registry post-marketing study for this new NDA now under review. The drug inhibits clotting factor X in its activated form, this inhibiting blood clotting. There is no "antidote" - treatment that can directly reverse the anticoagulant effects, thus bleeding can be a problem to stop.

2 possible clinical studies to characterize drug safety better after approval:

- Registry of major bleeding events occurring on drug therapy
- Development of a means of "reversing" - or mitigating - major bleeding in patients receiving the drug

(Nothing like these possible proposals was done on Dabigatran.)

DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Internal Team mtg
INDICATION: for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery
PURPOSE: edit/discuss labeling
EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059
Global Submit: \\CDSESUB1\EVSPROD\NDA022406\022406.enx

NDA 22406: Xarelto (Rivaroxaban) Tablets: - Sponsor - J&J. for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery.

Anticipated Action: TBD ***Press Release: TBD*** ***BURST: TBD***

Project Manager	Clinical Team	Medical Officer	Statistics Reviewer	Chemistry/ Biopharm	Pharm/Tox Reviewer	Microbiology Reviewer	Clin.Pharm. Reviewer

	Leader			Reviewer			
Newman Tyree	Kathy Robie-Suh	Min Lu	Xu, Qing	Crich, Joyce Ghosh, Tapash	Chopra, Yash M	N/A	Grillo, Joseph

Letter Date: December 30, 2010 **AC Mtg TBD**
Receipt Date: January 3, 2011
Date to DD: June 23, 2011
PDUFA Date: July 3, 2011
Action Package Delivery Date: TBD

SIGNATURE OF REQUESTER Tyree Newman	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

TYREE L NEWMAN
06/16/2011

Newman, Tyree

From: Newman, Tyree
Sent: Tuesday, June 14, 2011 12:58 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 PMR/PMC

Good day Andrea, please see the proposed post marketing trial requests from our review team regarding NDA 22406. Please review and respond by Friday, June 17, 2011, if you have any questions or comments. We have also proposed completion dates. If you cannot meet the proposed dates, please propose alternative dates and we will confirm if we are in agreement with your proposal. Also, you can expect additional post marketing requests. Once I receive these requests, I will forward immediately.

Postmarketing Commitments (PMC) for Rivaroxaban:

Develop and propose a 5 mg dosing form (tablet) or scored 10 mg tablet to allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically relevant changes in rivaroxaban exposure. The 5 mg dose form should be sufficiently distinguishable from the 10 mg tablet in physical characteristics. Full chemistry, manufacturing and controls (CMC) information for the 5 mg dosage form including the batch data and stability data, labels, updated labeling, and updated environmental assessment section is required in a prior approval supplement.

Rationale

A 5 mg dosing form (tablet) or scored 10 mg tablet will allow for proper dose titration when rivaroxaban needs to be co-administered in patients at risk for clinically significant changes in rivaroxaban exposure. These include patients with Child Pugh class B hepatic impairment without coagulopathy, patients concurrently taking rivaroxaban with a Pgp and strong CYP3A4 inhibitor, and patients concurrently taking rivaroxaban with a P-gp and mild or moderate CYP3A4 inhibitor with mild-moderate renal impairment. The availability of lower dose strengths of rivaroxaban is the best option to allow a larger patient population to receive this treatment.

Proposed completion dates

- Final Protocol Submission: 8/17/2011
- Study Trial Completion: 3/3/2012
- Final Report Submission: 4/3/2012

Postmarketing Requirements (PMR) for Rivaroxaban:

Evaluate the effect of renal impairment (i.e., mild, moderate, severe) plus the concurrent use of P-gp and moderate inhibitors of CYP3A4 on the pharmacokinetics, pharmacodynamics, and safety of rivaroxaban in volunteers so that appropriate dosing recommendations can be developed in these populations following the development of the 5 mg tablet formulation.

Rationale

You reported that based on simulations using a population pharmacokinetic approach, you anticipate that combined use of a drug that would inhibit non-renal clearance by 30% and inhibit active renal clearance by 45% in patients with mild or moderate renal impairment may result in an approximate 2 and 2.4 fold increase in plasma AUC, respectively, when compared to subjects which is considered significant. Using a physiologically based (PBPK) modeling approach FDA reached similar results, but also found that this complex DDI may be more pronounced in the elderly.

Proposed completion dates

- Final Protocol Submission: 7/18/2011
- Study Trial Completion: 2/3/2012
- Final Report Submission: 3/3/2012

If you have any questions, please let me know.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

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/s/

TYREE L NEWMAN
06/15/2011

Newman, Tyree

From: Newman, Tyree
Sent: Monday, June 13, 2011 11:35 AM
To: 'Kollath, Andrea [PRDUS]'
Cc: 'Jalota, Sanjay [PRDUS]'
Subject: RE: NDA 22406 FDA label review
Attachments: NDA 22406 (b) (4)100-count-blister-pack.pdf; NDA 22406 draft-carton-and-container-labels-bottle.pdf; NDA 22406 draft-carton-and-container-labels- (b) (4)bl.pdf

Hi Andrea, please also see our comments regarding the container carton and blister pack labels. Please accept changes you agree to and for changes you do not, keep in track changes.

Please provide your response by Thursday, COB, June 16, 2011.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
10903 New Hampshire Ave.
Silver Spring, MD 20993
301-796-3907 (phone)
301-796-9845 (fax)
Tyree.Newman@fda.hhs.gov

From: Newman, Tyree
Sent: Monday, June 13, 2011 11:22 AM
To: Kollath, Andrea [PRDUS]
Cc: Jalota, Sanjay [PRDUS]
Subject: NDA 22406 FDA label review

Good morning Andrea, please see the attached redlined version of the label regarding NDA 22406 for your review and comments. Please accept changes you agree to and for changes you do not, keep in track changes.

Please provide your response by Thursday, COB, June 16, 2011.

Kind regards,

Tyree

Tyree Newman
Regulatory Project Manager
Food and Drug Administration
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/s/

TYREE L NEWMAN
06/15/2011

Newman, Tyree

From:	Newman, Tyree
Sent:	Monday, June 13, 2011 11:22 AM
To:	Kollath, Andrea [PRDUS]
Cc:	Jalota, Sanjay [PRDUS]
Subject:	NDA 22406 FDA label review
Attachments:	NDA 22406 label comments_6 13 11.doc

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Please provide your response by Thursday, COB, June 16, 2011.

Kind regards,

Tyree

Tyree Newman
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/s/

TYREE L NEWMAN
06/15/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OSE**			FROM: Tyree Newman, RPM, Division of Hematology Products	
DATE May 25, 2011	IND NO. N/A	NDA NO. 22406	TYPE OF DOCUMENT Label	DATE OF DOCUMENT May 25, 2011
NAME OF DRUG Xarelto (Rivaroxaban)	PRIORITY CONSIDERATION Rush		CLASSIFICATION OF DRUG Anticoagulant	DESIRED COMPLETION DATE June 13, 2011

NAME OF FIRM: Johnson and Johnson

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- X FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
We request any comments on the labeling regarding possible hepatic effects specifically to the sponsor's proposed labeling sections 6.2 and 8.7. Also, we are willing to accept comments regarding any other sections of the label.

The label is currently being reviewed by the review team.

DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Internal Team mtg
INDICATION: for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery
PURPOSE: edit/discuss labeling
EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059
Global Submit: \\CDSESUB1\EVSPROD\NDA022406\022406.enx

NDA 22406: Xarelto (Rivaroxaban) Tablets: - Sponsor - J&J. for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery.

Anticipated Action: TBD ***Press Release: TBD*** ***BURST: TBD***

Project Manager	Clinical Team Leader	Medical Officer	Statistics Reviewer	Chemistry/ Biopharm Reviewer	Pharm/Tox Reviewer	Microbiology Reviewer	Clin.Pharm. Reviewer
Newman Tyree	Kathy Robie-Suh	Min Lu	Xu, Qing	Crich, Joyce Ghosh, Tapash	Chopra, Yash M	TBD	Grillo, Joseph

Letter Date:	December 30, 2010	**AC Mtg TBD**
Receipt Date:	January 3, 2011	
Date to DD:	June 23, 2011	
PDUFA Date:	**July 3, 2011**	
Action Package Delivery Date:	**TBD**	

SIGNATURE OF REQUESTER Tyree Newman	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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TYREE L NEWMAN
05/25/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

COMPLIANCE REVIEW

DATE: May 24, 2011

TO: Tyree Newman, Regulatory Project Manager
Min Lu, M.D., Medical Officer
Division of Hematology Products

FROM: Susan D. Thompson, M.D., Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-406

APPLICANT: Johnson & Johnson

DRUG: Xarelto (rivaroxaban)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: 1. Prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery

CR LETTER DATE: May 27, 2009

(b) (4) AUDIT SUBMISSION DATE: April 19, 2010

(b) (4) INFORMATION REQUEST RESPONSE DATE: September 26, 2010

CR SUBMISSION DATE: December 23, 2010

I. BACKGROUND: Rivaroxaban is a highly selective direct factor Xa (FXa) inhibitor for oral administration. Inhibition of FXa produces antithrombotic effects by decreasing the amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting existing thrombin levels. The sponsor states that the remaining thrombin should be sufficient to ensure primary hemostasis, resulting in a favorable efficacy to safety (bleeding) margin for rivaroxaban. The sponsor submits this NDA to support the use of rivaroxaban for the indication of prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.

Patients undergoing major orthopedic surgery, including total hip replacement (THR) and total knee replacement (TKR) surgeries, are a group that is at a particularly high risk for venous thromboembolism (VTE), which includes DVT and PE. Without prophylaxis, the incidence of objectively confirmed total DVT based on older studies is approximately 40 to 60% following THR or TKR, with a 10-30% incidence of proximal DVT. The most appropriate strategy to reduce the incidence of VTE is prophylaxis for all patients undergoing THR or TKR. Current therapeutic agents available for anticoagulant prophylaxis include low molecular weight heparins (LMWHs), fondaparinux, and adjusted-dose vitamin K antagonists such as warfarin. The duration of therapy is at least 10 days for both THR and TKR; for patients undergoing THR, extended prophylaxis to up to 35 days after surgery is recommended. LMWHs and fondaparinux are administered subcutaneously, which may be associated with pain and bruising as well as poor compliance. Warfarin is the only available oral anticoagulant for VTE prophylaxis after major orthopedic surgery in the U.S. However, warfarin has a narrow therapeutic window, exhibits variable dose response, has many dietary and medicinal interactions, requires dose adjustment, and has a slow onset of action. Rivaroxaban offers an alternative oral prophylactic therapy for VTE.

IND 64,892 for rivaroxaban was submitted on May 29, 2002 for the treatment and secondary prophylaxis of VTE by Bayer. All of the clinical trials submitted with the current NDA were conducted by Bayer. Approximately one month prior to the submission of this NDA, Bayer sold the rights of reference for use of the investigations to Johnson and Johnson. Johnson and Johnson submitted NDA 22-406 as the applicant on July 28, 2008. Of note, both Bayer and Johnson and Johnson submitted letters to the review division that the IND is now transferred to Johnson and Johnson.

The pivotal protocols in support of NDA 22-406 were:

RECORD 1 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; controlled, double-blind, randomized study of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 11354)

RECORD 2 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; controlled, double-blind, randomized study of BAY- 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 11357)

RECORD 3 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 in the prevention of VTE in patients undergoing elective total knee replacement (Protocol 11356)

RECORD 4 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement (Protocol 11355)

FDA Inspections

During the conduct of the clinical studies for this NDA, complaints were received regarding two investigators enrolling subjects, Dr. Arturo Corces in RECORD 2 and Dr. David Loucks in RECORD 4. A Warning Letter was issued to Dr. Corces on May 22, 2008 who enrolled subjects in RECORD 2 for failure to personally conduct or supervise the clinical investigations, failure to meet informed consent requirements, failure to ensure that studies were conducted according to the relevant current protocol, failure to maintain adequate and accurate case histories, and failure to maintain adequate drug disposition records. The Warning Letter to Dr. Corces from DSI recommended the data contributed to RECORD 2 by Dr. Corces be considered unreliable.

A NIDPOE was issued on August 18, 2009 for Dr. Loucks, who enrolled subjects in RECORD 4. The OAI-NIDPOE letter describes failure to adhere to the protocol, inadequate/inaccurate records, failure to report to the IRB risk to human subjects or others, submission of false information, and failure to supervise/personally conduct a study. On June 3, 2008, after discussion with the review division regarding the inspectional findings, Bayer notified the review division that due to falsification and systematic failures of the outpatient source data, that data from Dr. Loucks' site should be excluded from the per protocol analysis. On the same date, Bayer notified the review division of a second RECORD 4 clinical investigator, Dr. Ricardo Esquivel in Naulcapan, Mexico, with issues impacting data integrity. These issues included inability to confirm from the source record that study medication was administered per protocol during the hospitalization periods, due to systematic discarding of medical records documenting study drug administration.

On July 28, 2008, Johnson & Johnson submitted the data from the RECORD 1, 2, 3, and 4 studies to the FDA to support the approval of rivaroxaban for the indication of prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery (NDA 22-406). After receipt of the NDA, eight FDA data validation inspections of investigators who enrolled subjects in the four RECORD studies were conducted. The results of these clinical investigator inspections resulted in the identification of multiple regulatory violations from many of these sites, raising concerns with the overall integrity of the data submitted for approval of the NDA. Details of the first cycle of clinical investigator, sponsor, and applicant inspections, as well as RECORD 1-4 investigators identified as problematic prior to submission of the NDA, are summarized in the following table:

Table 1: NDA 22-406 Pre-NDA and First Cycle Clinical Investigator Data Validation Audits

Name of CI or Sponsor Location	Protocol # and # of Subjects	Major Findings	Inspection Date	Interim Classification	DSI Classification
Andrzej Gorecki Szpital Kliniczny Dzieciatka Jezus – Centrum Leczenia Obrazen Klinika Ortopedii I Traumatologii Narzadu Ruchu Ul. Lindleya 4 02-005 Warszawa , Poland	Protocol #11354, RECORD 1 Site # Poland 18006 # of subjects (Total #: 71): Xarelto: 36 Enoxaparin: 35	None	1/9–1/23/09 (complaint related)	NAI	NAI
Tadeusz Gazkzik Slaska Adademia Medyczna Katedra I Oddzial Kliniczny Ortopedii'Wojewodzki Szpital Specjalistyczny Nr 5 Im. Sw. Barbaby Pl. Medykow 1 41-200 Sosnowiec, Poland	Protocol #11354, RECORD 1 Site # Poland 18012 # of subjects (Total #: 76): Xarelto: 38 Enoxaparin: 38	None	2/2-2/6/09	NAI	NAI
Arturo Corces 7340SW 79th Street Miami Institute for Medical Research Miami, FL 33186	Protocol #11357, RECORD 2 Site # 14012 # of subjects (Total #: 19): Xarelto: 9 Enoxaparin: 10	Failure to supervise, informed consent, protocol, recordkeeping and drug disposition deficiencies	3/20 – 4/26/07 (complaint related)	OAI	OAI (WL)
Qingming Yang Rui Jin Hospital, Shanghai Second Medical University Orthorpaedic Department Shanghai Ryuijin Hospital No. 197 Ruijin Second Road Shanghai, China 200025	Protocol # 11357, RECORD 2 Site # China 54005 # of subjects (Total# 34): Xarelto: 17 Enoxaparin: 17	AEs not reported, including abnormal liver function tests and bleeding; protocol violations, recordkeeping deficiencies	2/9-2/13/09	OAI	OAI (untitled)
Cesar Diaz Valverde Hospital Edgardo Rebagliati Martins Av. Edgardo Rebagliati Martins S/N Jesus Maria Lima Lima, 11 Peru	Protocol # 11357, RECORD 2 Site # Peru 64005 # of subjects (Total#: 41): Xarelto: 20 Enoxaparin: 21	AEs (relatively minor) not reported; protocol and recordkeeping deficiencies	1/26-1/30/09	VAI	VAI

Table 1: NDA 22-406 Pre-NDA and First Cycle Clinical Investigator Data Validation Audits

Name of CI or Sponsor Location	Protocol # and # of Subjects	Major Findings	Inspection Date	Interim Classification	DSI Classification
Binfang Zeng Affiliated Sixth People's Hospital Orthorpaedic Department No. 600 Yishan Road, Xuhui District Shanghai, China 200233	Protocol # 11356, RECORD 3 Site # China 54014 # of subjects (Total# 26): Xarelto: 13 Enoxaparin: 13	AEs not reported, including 2 SAEs; protocol violations	2/15-2/19/09	OAI	VAI
Jacek Kruczynski Szpital Uniwersytecki im. Antoniego Jurasze Klinika Ortopedii i Traumatogii Narzadu Ruchu Ul. M. Sklodowskiej-Curie 9 85-094, Bydgoszcz Poland	Protocol # 11356, RECORD 3 Site # Poland 18003 # of subjects (Total# 36): Xarelto: 18 Enoxaparin: 18	Protocol violations	1/26-1/30/09	VAI	VAI
David Loucks 14100 E. Arapahoe Rd. Suite B370 Centennial, CO 80112	Protocol # 11355, RECORD 4 Site # 14012 # of subjects (Total# 94): Xarelto: 46 Enoxaparin: 46	Recordkeeping deficiencies and falsification, IRB reporting, protocol and informed consent deficiencies	4/15-7/08	OAI	OAI (NIDPOE)
Ricardo Esquivel Naulcapan, Mexico	Protocol # 11355, RECORD 4 Site # 32006 # of subjects (Total# 42): Xarelto: 22 Enoxaparin: 20	Drug disposition, record deficiencies, missing records	Identified by Bayer (not inspected by FDA)	NA	Data not usable
R. Michael Murray Capstone Clinical Research 2018 Brookwood Medical Center Suite 314 Birmingham, AL 35209	Protocol # 11355, RECORD 4 Site # 14005 # of subjects (Total # 152) Xarelto: 76 Enoxaprin: 76	Post-operative randomization in violation of protocol, possible unblinding	2/17-2/26/09	OAI	OAI-WL
David Fox Unlimited Research, LP 12709 Toepperwein Road	Protocol #11355, Record 4 Site #14022 # of subjects	Informed consent deficiencies and protocol violations	1/26-1/28/09, 2/2-2/6/09, 2/12-2/13/09	VAI	VAI

Table 1: NDA 22-406 Pre-NDA and First Cycle Clinical Investigator Data Validation Audits					
Name of CI or Sponsor Location	**Protocol # and # of Subjects**	**Major Findings**	**Inspection Date**	**Interim Classification**	**DSI Classification**
Suite 101 San Antonio, TX 78233	(Total # 64) Xarelto: 32 Enoxaparin: 32				
Bayer Pharmaceutical 340 Change Bridge Rd. Pine Brook, NJ 07058	Protocol # 11354, RECORD 1 Protocol # 11357, RECORD 2 Protocol # 11356, RECORD 3 Protocol #11355, Record 4	Monitoring deficiencies, protocol violations, failure to ensure that FDA was informed of all AEs	2/24-2/27, 3/3-3/6, 3/9, 3/11-3/13, 3/16-3/19, 3/26, 3/30-3/31/09	VAI	VAI
Johnson & Johnson 920 U.S. Highway 202 Raritan, NJ 08869-0602	Protocol # 11354, RECORD 1 Protocol # 11357, RECORD 2 Protocol # 11356, RECORD 3 Protocol #11355, Record 4	No significant issues noted; however, inspection limited in scope	3/24/09	NAI	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

As can be seen in Table 1, there were a variety of major findings, including protocol violations, deficiencies in drug dispensation records, AE reporting, and informed consent. A major issue identified during inspections of RECORD 4 study sites was post-operative randomization of subjects, instead of randomization of subjects prior to surgery as specified in the protocol. In order to characterize more fully how frequently post-operative randomization in violation of the protocol occurred, an assignment for inspection of three additional clinical investigators in RECORD 4 was issued. Details of the second cycle of clinical investigator inspections are summarized in the following table:

Table 2: NDA 22-406 Second Cycle Clinical Investigator Data Validation Audits

Name of CI/Address/contact information	Protocol # and # of Subjects	Major Findings	Inspection Date	Interim Classification	Final Classifiation
Dr. John Ward Capstone Clinical Research 2018 Brookwood Medical Center Suite 314 Birmingham, AL 35209 Phone: (205) 877-2766 Fax: (205) 877-2990 Email: capstoneclin@aol.com	Protocol # 11355 RECORD 4 Site # 14010 # of subjects (Total # 203) Xarelto: 101 Enoxaprin: 102	Post-operative randomization, IRB approval expired	5/12-5/20/09	OAI	OAI-WL
Dr. Craig Buettner West Alabama Research, Inc. Black Warrior Medical Building 100 Rice Mine Road Loop Suite 104 Tuscaloosa, AL 35406 Phone: (205) 248-6160 FAX: (205) 248-6467 Email: vredding @walresearch.com (coordinator)	Protocol #11355 RECORD 4 Site #14004 # of subjects (Total # 61) Xarelto: 31 Enoxaprin: 30	Post-operative randomization	5/4-5/6/09	OAI	OAI-WL
Dr. John Schwappach Colorado Orthopedic Consultants 401 W. Hampton Place Suite 220 Englewood, CO 80110 Phone: (303) 695-6060 (research dept. extension) FAX: (303) 399-9959 Email: schwappach@cocortho.com	Protocol #11355 RECORD 4 Site #14045 # of subjects (Total # 106) Xarelto: 53 Enoxaprin: 53	Protocol violations	5/5-5/19/09	VAI	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

Additionally, inspection of Bayer Pharmaceuticals as the sponsor of the four RECORD 4 studies revealed that the sponsor failed to 1) ensure proper monitoring of the study, 2) to ensure the study was conducted in accordance with the protocol and/or investigational plan, and 3) to ensure that FDA and all investigators were promptly informed of significant new adverse effects or risks. The sponsor inspection of Bayer revealed that some of the minor items cited in the OAI letters for Drs. Corces and Murray were not identified in site Monitoring Visit Reports although the CRAs were aware of them (either through the company's internal audit program or FDA inspections). The major violations at these sites were not detected by sponsor monitoring. Bayer acknowledges the failure to include the cited deficiencies in

Monitoring Visit Reports in their response letter dated April 13, 2009. The sponsor inspection of Bayer does not provide information on whether or not monitoring and/or corrective actions were inadequate at other sites classified by FDA as OAI. A limited inspection of the applicant Johnson & Johnson revealed no identifiable deviations from applicant related regulations as per 21 CFR 314.

Complete Response Letter to Applicant and Subsequent Activity

On May 27, 2009 FDA issued an NDA Complete Response letter to Johnson & Johnson for Xarelto NDA 22-406 that listed several deficiencies, including Clinical Deficiency 1 which stated that the reasons that data from 7 Clinical Investigator sites are considered unreliable include:

- Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]
- Failure to report to the sponsor adverse events [21 CFR 312.64]
- Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the inspection [21 CFR 312.62 (b)]
- Failure to obtain adequate informed consent [21 CFR 50]
- Failure to maintain drug accountability records [21 CFR 312.62 (a)]
- Failure to report to the IRB all unanticipated problems involving risk to human subjects [21 CFR 312.66]

On the basis of these findings, FDA requested in the CR letter that the applicant:

a. Provide the following information regarding their QA audit program:
   i. A report of the QA audit plan, including the plan for securing compliance from non-compliant clinical investigators. Included should be copies of any Standard Operating Procedures that were in place during conduct of the study to address means by which corrective actions were to be taken if or when you or the CRO identified noncompliant clinical investigators.
   ii. A report of the sponsor's audit findings, including any corrective actions taken and final outcome for the Yang, Murray, Corces, Loucks, and Esquivel sites and for all other sites audited under the sponsor's QA program.
   iii. A description of any clinical investigators terminated for noncompliance. The list should include sites, specific violations, and whether the data were included in the NDA submission.

b. Describe Bayer's QA program with respect to the oversight of CROs that were hired to monitor the clinical sites, including (b) (4) for RECORD 4. Describe the procedures implemented to make sure that the CROs adequately monitored the clinical sites. The response should include the following information:
   i. Provide the procedures by which Bayer was kept apprised by the CROs concerning monitoring of the clinical site during the course of the study. Specifically, describe what information the CROs provided to the sponsor and provide a list of noncompliant clinical study sites reported by the CROs.
   ii. Describe how the sponsor reviewed the information provided by the CROs during the course of the study and at the end of the study. Describe what monitoring information was kept at the end of the study.

c. Independent Thirty Party Audits (b) (4)

Provide assurance that the clinical data obtained from the RECORD 1, 2, 3, and 4 studies are reliable. Specifically, perform an additional audit and supply the results of this audit within your response to this letter. Within your response, include:

i. A copy o f your audit plan, including the following information:
   - How many clinical sites were to be audited, how many subject records were examined, and a description of the process for selection of the audited sites.
   - If not all subject records at a given clinical site were to be audited, describe how subject records were sampled and how the specific data from each subject were audited.

ii. The timeline for completion of your audit (plan finalization, start date, completion date, report finalization date).

As per above, the CR letter stated that additional third party audits should be conducted to provide assurance that the RECORD 1-4 studies are reliable and requested that Johnson & Johnson submit a proposal for these audits. On June 8, 2009, Johnson & Johnson submitted "Clarification Questions" for the Complete Response Letter, which included a proposal that 24 new audits be conducted, together with submission of the reports of the 69 routine and 5 directed/for-cause audits. Johnson & Johnson proposed that the results of the new audits be submitted as an addendum to the Complete Response. In a written response preparatory to a face-to-face meeting between FDA and Johnson & Johnson on June 19, 2009, FDA proposed that 25% of the clinical investigator RECORD 1-4 sites be audited by an independent, third party. At the June 19, 2009 meeting, FDA proposed the following:

> "Selection of sites from all four RECORD studies with a total enrollment of 60 or higher results in identification of 26 sites: 9 in RECORD 1 (2 already inspected by the Agency), 4 in RECORD 2, and 13 in RECORD 4 (6 already inspected by the Agency). If 5% is the margin of error for tolerance of unreliable sites detected by the audit, then the audit of 30 sites is necessary to show with 95% confidence that the percentage of unreliable sites exceeds 5%, assuming that 25% of sites are actually unreliable. Therefore, 18 high enrolling sites not previously inspected could be included in the audit plan, which represents 11% of enrolled subjects. If 30 total sites are to be audited, an additional 12 sites could be included in the audit, which represent a random sample of sites which enrolled 40-60 subjects and sites which enrolled 10-30 subjects."

Johnson & Johnson submitted the proposed audit plan on July 8, 2009. The audit plan included audits of an additional 30 clinical sites across the entire RECORD program including all 18 high enrolling sites with $\geq$ 60 randomized subjects, and 12 moderate enrolling sites with 15-59 randomized subjects. The 12 moderate enrolling sites (3 per study) were randomly selected by the Johnson & Johnson statistics group from a pool of sites which met the stated enrollment criteria. None of the sites selected for audit had previously been inspected for this NDA by the FDA. Johnson & Johnson intended to audit all subjects if there were 35 subjects or less enrolled at the site. If there were more than 35 subjects, a random selection of subjects

was to be chosen such that if no data integrity issue was found in sample subjects, there would be 95% confidence to rule out more than a 5% error rate. The resulting sample size represented a 31% to 58% sampling (35 to 43 subjects) of sites which enrolled more than 35 subjects. Audit of these 30 sites resulted in a total of 950 subjects with data audited out of 12,729 subjects, which constituted 7.5% of all subjects in the RECORD program data base. The results of the (b) (4) audits were to be submitted with the CR.

The parameters to be verified during each audit were those contained in the Complete Response Letter (listed in Part II.1.c. below). The audit findings at each site were to be documented in an individual site audit report and provided to the FDA. In addition, a separate summary report was to be provided. Johnson & Johnson proposed that (b) (4) conduct the targeted audits. The criteria used by Johnson & Johnson to identify the independent third party auditor required that there were 1) no previous associations with the rivaroxaban development program, and 2) no current contracts with Johnson & Johnson or Bayer. Auditors utilized were full-time employees of the independent third party or regionally based contractors who were trained on the company's SOP and were overseen by a full-time employee of the independent third party. Johnson & Johnson has previously employed (b) (4) as an independent third party audit team. Johnson & Johnson proposed to provide a member of the Bayer Global Clinical Operations or Quality Assurance team to escort the third-party auditor for logistical support and translation, if needed.

On August 5, 2009, DSI communicated in writing that DSI was in agreement with the number of sites selected and the number of subjects to be audited at each site, submission of individual site reports as well as a separate summary report, and agreement with the proposed Data Verification Tool for the (b) (4) audits.

On March 5, 2010, Johnson & Johnson submitted Meeting Background Information in preparation for a face-to-face meeting on April 7, 2010. The Background Information contained a summary of the results of the (b) (4) audits. Johnson & Johnson also submitted a proposal for data verification and sensitivity analyses for RECORD 4 in order to allay concerns regarding the FDA inspectional and third party audit findings pertaining to that study. According to the proposal, Johnson & Johnson would employ (b) (4) to revisit all RECORD 4 sites to obtain unreported adverse events as well as relevant data for the sensitivity analysis. DSI responded that a review of the complete audit reports conducted for all four RECORD studies, rather than a summary, was necessary before agreement could be reached on a path forward. In addition, no recommendation could be given regarding the (b) (4) data verification proposal prior to the review of the RECORD 4 (b) (4) audits. Subsequent to this meeting, Johnson & Johnson submitted on April 19, 2010 the (b) (4) audit reports for the audits conducted between July 27, 2009 and October 16, 2009, as well as copies of the Bayer internal company audits conducted concurrently with the clinical trials. The CR was submitted on December 23, 2010.

The following sections of this review will first evaluate the Applicant's Complete Response focusing on the adequacy of responsiveness to the items requested in the Agency's Complete Response Letter. This will be followed by a description of (b) (4) Audit findings focusing on items considered key to evaluation of data reliability. The review will then provide DSI's analysis of the specific audit findings and their impact on data reliability, followed by an

assessment of data reliability for each RECORD study. The review will then conclude with DSI's conclusions and recommendations on reliability of data for the application as a whole.

II. EVALUATION OF APPLICANT'S DECEMBER 23, 2010 SUBMISSION

In the FDA's April 29, 2009 Complete Response (CR) letter, a number of requests were outlined that the applicant needed to address to resolve the Agency's concerns with respect to data integrity issues. In the sections below, each of the items in the letter will be restated in bold font, followed by a summary of Johnson & Johnson's response, and DSI's assessment of the adequacy of the response.

1. a. Provide the following information regarding your clinical data quality assurance (QA) audit program that was in place for the four RECORD studies:

i. A report of your QA audit plan, including your plan for securing compliance from non-compliant clinical investigators. Include copies of any standard Operating Procedures (SOPs) that were in place during conduct of the study to address the means by which corrective actions were to be taken if or when you or the applicable means by which corrective actions were to be taken if or when you or the applicable contract research organization (CRO) identified noncompliant investigators.

Johnson & Johnson provided a summary of their audit plans for the RECORD 1, 2, 3, and 4 studies. They also provided a summary of their audit procedures and copies of SOPs for audit procedures. Included were SOPs which address procedures for site initiation and monitoring, study management, investigator site audits, and misconduct.

DSI Assessment of Response: Johnson & Johnson has adequately responded to this request.

ii. A report of your audit findings, including any corrective actions taken and final outcomes for the Yang, Murray, Corces, Loucks, and Esquivel sites and for all other sites you audited under your QA program.

iii. A description of any clinical investigators terminated for non-compliance. Provide a list of these clinical investigators, their sites, the specific violations, and whether the data were included in the NDA submission.

The description of the findings requested in Parts 1.a.ii. and 1.a.iii. and the DSI assessment of these findings are combined below.

Response to 1a.ii.

Johnson & Johnson provided a summary of audit findings, corrective action plans, and outcomes for each site for clinical investigator sites that participated in the RECORD studies. There were 74 clinical investigator site audits conducted by Bayer; 69 were routine and 5 were for cause. There were 25 audits conducted at RECORD 1 sites, 15 audits conducted at RECORD 2 sites, 15 audits conducted at RECORD 3 sites, and 19 audits conducted at RECORD 4 sites. Findings during the audit were classified into Class 1, Class 2, and Class 3. Class 1 findings are findings of confirmed misconduct which endanger subject safety and/or

would lead to rejection of data by Regulatory Authorities, whereas Class 2 and Class 3 are less serious findings. There were 2 clinical investigator sites with Class 1 findings in RECORD 1, 1 clinical investigator site with Class 1 findings in RECORD 2, 3 clinical investigator sites with Class 1 findings in RECORD 3, and 2 clinical investigators with Class 1 findings in RECORD 4. Of these clinical investigator sites with Class 1 findings, 4 were the sites which were for cause inspections: Dr. Macaire Site 11354 in RECORD 1 and Site 16009 in RECORD 3, Dr. Mortele Site 28020 in RECORD 3, Dr. Dadi Site 60017 in RECORD 4, and Dr. Loucks Site 14029 (the third inspection); these inspections will be discussed below. The remaining sites with Class 1 findings included Dr. Jasey Site 26007 in RECORD 2 which had enrollment temporarily suspended due to limited access of the site by the auditors to source documents, poorly documented changes to source documents, suboptimal level of principal investigator involvement, and enrollment of a clearly ineligible subject. Enrollment was restarted 11 days later after these issues were addressed to the satisfaction of the sponsor. The 2 remaining sites with a Class 1 finding both routinely obtained coagulation studies at the site, which could potentially result in unblinding and is a protocol violation. Both sites (Dr. Schmelz Site 10010 in RECORD 1 and Dr. Debue Site 16001 in RECORD 3) corrected the problem immediately. The last site with a Class 1 finding is Dr. Esquivel Site 32006, also discussed below.

FDA requested a report of the applicant's audit findings, including any corrective actions taken and final outcomes for the Yang, Murray Corces, Loucks, and Esquivel sites and for all other sites that were audited under their QA program. The following provides a summary of this information.

Dr. Q. Yang Site 54005 RECORD 4: This site was not included in Bayer's audit program. The regulatory violations cited by the FDA inspector are acknowledged by the applicant in the CR and reasons given for the violations. However, no evidence is presented to refute the violations observed during FDA inspections.

Dr. Michael Murray Site 14005 RECORD 4: There were no Class 1 findings at the inspections of Dr. Murray, Site 14005, and Dr. John Ward, Site 14010, who enrolled as separate sites in Birmingham, Alabama under the umbrella of an SMO. Class 2 findings included source data inadequacies, systematic data inaccuracies involving adverse event and concomitant medications, and failure to obtain protocol required venograms. The applicant presents information from Dr. Murray's letter of response to the inspectional findings. The source document issues were addressed by source verification by the site CRA, with correction as needed. These issues differ from those identified during the FDA clinical site inspection (postoperative randomization, possible unblinding) which resulted in an OAI Warning Letter.

Dr. Craig Loucks Site 14029 RECORD 4: A routine audit of this site was conducted starting on December 12, 2006. A number of Class 2 findings were identified involving problems with data quality and general GCP compliance, including lack of source documentation and lack of documentation of Principal Investigator (PI) involvement. Study activities were inappropriately delegated to unqualified study personnel, and there were extensive delays in CRF completion. Enrollment was placed on hold at the conclusion of the inspection; enrollment resumed on January 16, 2007 based on feedback from the CRA monitoring the

study. A follow-up audit was conducted starting on May 14, 2007 to determine the effectiveness of the corrective actions taken. Persistent GCP noncompliance was noted, including evidence that the original source data worksheets completed during the outpatient phase of the study had been rewritten and the original documents not maintained. Enrollment was placed on hold, and the frequency of monitoring was increased. A third audit was conducted starting January 16, 2008. This audit was precipitated by site notification to the IRB of data falsification; the IRB communicated this information to the FDA. The January, 2008 Bayer audit confirmed falsification of the signatures of the PI (and in some cases the sub-investigator) on lab reports, ECGs, hospital orders, FDA 1572s, SAE documentation, IRB submissions, and ICF documents. At least 19 patients' source data and nine submissions to the IRB were falsified.

For the NDA submission, subjects from Dr. Loucks' site were excluded from the per protocol analyses. Patients were included in the safety and mITT analyses when validity criteria were met, and sensitivity analyses were conducted after including subjects in the per protocol analysis and excluding subjects in the mITT which revealed that the overall results were not changed.

Response to 1.a.iii.

Johnson & Johnson listed the following clinical investigators who were terminated for noncompliance:

Dr. Esquivel Gomez Site 32006 RECORD 4: A routine audit of the site starting on October 17, 2007 revealed the Class 1 finding that the site had failed to retain all available source records due to a hospital policy of periodically purging hospital and in-patient nursing notes. The nursing notes were considered to be source documents which verified the administration of the investigational product. The site had been placed on enrollment hold by the study team on August 9, 2007 due to delays in CRF completion and the hold remained in effect for the remainder of the study.

Subjects were included in the Per Protocol analyses only when it could be confirmed that eCRF data had been verified as correct by the CRA. All subjects were included in the safety and mITT populations unless the subject did not meet validity criteria.

Dr. Arturo Corces Site 14010 RECORD 2: This site was not audited by Bayer. The inspection conducted by FDA found inadequate Investigator oversight and systematic use by the site of PlexiPulse pneumatic compression, which was not allowed by the protocol. An Investigative Committee was established and follow-up activities were conducted by Bayer, including assignment of an additional CRA to the site. Retraining was conducted. No subjects randomized were valid for the per protocol analysis due to the use of pneumatic compression or inadequate assessment of thromboembolism. All subjects were included in the safety and mITT analyses, unless they did not meet validity criteria.

Dr. Richard Rouhe Site 14062 RECORD 4: On August 16, 2007 Dr. Rouhe was notified by his IRB of his failure to report that his medical license was on probation for 5 years by the California Medical Board. Upon transmission to Bayer of this information, enrollment at this

site was terminated; six subjects had been randomized and two subjects were treated. The CRA noted that Dr. Rouhe's CV and medical license were missing at the first periodic monitoring visit on May 30, 2007; however, copies of the license was available at the August 10, 2007 CRA visit, and his CV was available at the October 15, 2007 monitoring visit. Data from this site were only included in the Safety Analysis, as the two subjects did not have an adequate assessment of venous thromboembolism.

Additionally, the efficacy data from Dr. P. Macaire's site 16009 in RECORD 1 was invalidated after a for cause inspection revealed that the CRA entered data in the eCRF and made changes outside of agreed permissible clarifications. The PI refused to confirm data entered into the eCRF. The data was considered valid for safety.

DSI Assessment of Response: Johnson & Johnson has adequately responded to this request. In general, review of the audits revealed that appropriate corrective action plans were generated and implemented for those clinical investigator sites with Class 1 findings. However, there were several areas of concern identified. Although significant findings were identified at Dr. Michael Murray's site during the Bayer audit, the issues identified by FDA inspectors which resulted in an OAI classification were not identified. Of greater significance, the initial two Bayer audits at Dr. Craig Loucks site identified significant problems at this site, resulting in a temporary hold on enrollment and increased frequency of monitoring. However, the most serious issue of forging the principal investigator's signature was apparently not identified during the two audits; it came to attention after a CRA at the site reported this violation to the IRB. The information available from the Bayer audits confirms the FDA's finding that data from the sties of Drs. Yang, Murray, Loucks, Corces, and Esquivel are not considered reliable.

b. Describe Bayer's QA program with respect to the oversight of CROs that were hired to monitor the clinical sites, including (b) (4) for the RECORD 4 study. Describe the procedures implemented to make sure that the CRO adequately monitored the clinical sites. In your response, include the following information:

i. How was Bayer kept apprised by the CROs concerning monitoring of the clinical sites during the course of the study? Specifically, what information did the CROs provide? Provide a list of non-compliant study sites reported by the CROs.
ii. How did Bayer review the information obtained from the CROs, during the course of the study and at the end of the study? What monitoring information was kept at the end of the study?
iii. What actions did Bayer take based on the monitoring reports?

Response to 1.b.i.-iii.
Bayer provided the majority of the monitoring for the RECORD 1, RECORD 2, and RECORD 3 clinical trials. The applicant presents information on the CROs that provided monitoring for RECORD 1 in Israel, RECORD 2 in Portugal and India, and RECORD 3 in Israel due to the lack of Bayer monitoring facilities in these countries. The monitoring oversight of the CRO

and processes for study documentation by the CROs were described for each of the non-Bayer CROs.

(b) (4) provided the monitoring for most RECORD 4 sites. Monitoring of RECORD 4 sites in Pakistan was provided by (b) (4) (by a subcontract (b) (4)) and by (b) (4) in Israel. The following information regarding (b) (4) role in RECORD 4 was presented:

- (b) (4) was responsible for the monitoring and management of RECORD 4.
- The Bayer Study Manager was responsible for overseeing the operational conduct of the CRO. This oversight included reviewing, tracking, analyzing, and summarizing the study related activities and the performance of (b) (4). The Bayer Study Manager kept the Bayer Study Team and relevant member of Bayer management informed of the overall progress of the study via meetings or reports.
- (b) (4) had a Project Leader responsible for the overall management of the trial, managed by the (b) (4) Director of Clinical Operations.
- Processes implemented to ensure sufficient oversight of outsourced trials and to ensure the CRO adequately monitored the clinical sites.
    - Holding the Study Kick-off Meeting chaired by the Bayer Study Manager
    - The Task Definition Document (TDD) detailed the expectations of each task from initiating and conducting through closing out the clinical trial. An outline of expectations of Bayer and (b) (4) responsibilities was included in this document. The TDD detailed project management, study management, monitoring, medical management, and electronic data transfer/data management.
    - Routine meetings between Bayer and (b) (4) were conducted.
    - Generation of a Monthly Status Tracking Report to track details of the study
- A Monitoring Plan was created by (b) (4) for RECORD 4, reviewed, and agreed upon by the Bayer Study Manager. The Monitoring Plan detailed roles, responsibilities, training plan, lines of communication (within (b) (4) external to sites), monitoring, and site management expectations.
- All CRAs were trained on the Monitoring Plan, study documents, goals, and timelines. CRAs were the primary contact with the sites, maintained the Investigator Site Files within (b) (4) and informed the (b) (4) Project Leader of any site issues.
- (b) (4) was responsible for ensuring appropriate training and supervised monitoring activities.
- (b) (4) Lead CRAs or Project Leader reviewed and approved Monitoring Reports. They ensured proper follow up and resolution of issues. The Monitoring Visit Reports were posted on the (b) (4) website, and the Bayer Study Manager had access to this website. Bayer did not conduct routine reviews of the (b) (4) Monitoring Visit Reports as this task was assigned to the (b) (4) Lead CRA or Regional Project Leader. The applicant states that discussion of issues identified at Monitoring Visits were discussed at "frequent meetings" between (b) (4) and Bayer.

DSI Assessment of Response: Johnson & Johnson has adequately responded to this request.

The methodology outline for Bayer's oversight of CROs used for the RECORD studies including (b) (4) should have been adequate. However, there are clearly monitoring inadequacies in the RECORD studies, most prominently in RECORD 4 which was monitored by (b) (4). Although there were meetings between (b) (4) and Bayer, there was no routine exchange of problematic information regarding audit findings (nor was this required by the agreements between (b) (4) & Bayer). In addition, as discussed above, critical issues identified by other means (FDA inspections, third party audits) were not routinely identified by (b) (4) site monitoring. This raises concerns, particularly, as to the adequacy of monitoring of RECORD 4 studies.

c. Independent Thirty Party Audits (b) (4)

The following was requested in the CR letter:

Provide assurance that the clinical data obtained from the RECORD 1, 2, 3, and 4 studies are reliable. Specifically, perform an additional audit and supply the results of this audit within your response to this letter. Within your response, include:

- **i. A copy o f your audit plan, including the following information:**
  - **How many clinical sites were to be audited, how many subject records were examined, and a description of the process for selection of the audited sites.**
  - **If not all subject records at a given clinical site were to be audited, describe how subject records were sampled and how the specific data from each subject were audited.**
- **ii. The timeline for completion of your audit (plan finalization, start date, completion date, report finalization date).**
- **iii. In addition to any other information within your audit report, address the following questions or requests:**
  - **At each site audited, how many violations involved each of the following specific issues? For each specific violation, list the clinical sites involved and provide a breakdown by treatment group for each site and overall for the four RECORD studies.**
    - **Enrollment of subjects that did not meet study eligibility criteria.**
    - **Failure of the Principal Investigator to ensure that all associates and colleagues assisting in the investigation were meeting the commitments of the study protocol.**
    - **Failure to report adverse events and serious adverse events**
    - **Failure to randomize subjects preoperatively**
    - **Failure to obtain informed consent from all subjects**
  - **List all clinical sites where either Bayer or CRO monitoring is determined to be ineffective, either in identifying significant violations or in taking actions towards securing compliance (such as notifying the sponsor).**

Response to 1c.i and ii.
Overview of (b) (4) Audits

The audit program was conducted by an independent third party, (b) (4). The studies included in the audit were the four pivotal Phase 3 studies of rivaroxaban 10 mg immediate-release tablets for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery. The objective of the audit program was to provide assurance that the data obtained from the RECORD 1-4 studies are reliable. The audits assessed compliance with the protocol and appropriate Good Clinical Practice (GCP) requirements. Additionally, compliance with International Conference on Harmonization (ICH) Guidelines, the U.S. Code of Federal Regulations as set out in 21 CFR Parts 50, 54, 56, and 312, and, where applicable, local regulatory requirements was assessed. Selected documentation including protocols and monitoring visit reports was provided to the auditors by Johnson & Johnson. Bayer clinical operations representatives assisted with logistics and translations. The audit program focused on the specific areas of concern identified by the FDA in the CR letter in six categories:

- Informed Consent
- Investigational Product
- Source Data Verification and Case Report Completion
- Safety
- Study Conduct
- Monitoring

Each audit observation was grouped by (b) (4) into one of the following categories:

CRITICAL: An observation that requires prompt corrective action to ensure compliance with regulations, guidelines, company policy, or local law. These findings if unaddressed could compromise human safety, market authorizations, or the acceptability of investigational product, data, facilities, or systems intended for regulatory submission. Regulatory authority action would appear probable.

MAJOR: An observation that requires improvement to ensure compliance with regulations, guidelines, company policy, or local law. These findings if unaddressed could compromise human safety, market authorizations, or the acceptability of investigational product, data, facilities, or systems intended for regulatory submission. Regulatory authority action would appear possible.

MINOR: An observation where improvement is recommended for minor deviations from regulations, guidelines, company policy, or local law.

There were 30 sites selected across the RECORD studies for auditing, including all 18 high-enrolling sites with $\geq$ 60 randomized subjects along with 12 moderate-enrolling sites with 15-59 randomized subjects. Focused audits were performed on individual subject records for 100% of the subjects enrolled in each site that had up to 35 subjects. The 12 moderate-enrolling sites (3 per study) were randomly selected by the Johnson & Johnson statistics group suing SAS Version 9.1 from a pool of all sites that met the stated enrollment criteria. For

higher enrolling sites, focused audits were performed on a random sample of 35 to 43 subjects, depending on the number of subjects required to rule out a 5% error rate or higher with 95% confidence. The 30 site audits were conducted between July 27 and October 16, 2009 by teams of 2 auditors for 28 sites and by 1 auditor for 2 sites. The number of audited sites and subjects by study and overall is shown below, taken from the sponsor's April 19, 2010 submission.

Table 3: NDA 22-406: (b) (4) RECORD Study Site Audits

Study	Audited sites/total sites	Audited subjects/total subjects at audited sites (%)	Audited subjects/total study subjects (%)
RECORD 1	11/217 (5.1% sites)	347/626 (55.4%)	347/4541 (7.6%)
RECORD 2	7/123 (5.7%)	216/439 (49.2%)	216/2509 (8.6%)
RECORD 3	3/147 (2.0%)	70/70 (100%)	70/2531 (2.8%)
RECORD 4	9/130 (6.9%)	312/636 (49.1%)	312/3148 (9.9%)
Overall	30/617 (4.9%)	945/1771 (53.4%)	945/12,729 (7.4%)

Draft (b) (4) audit reports were reviewed by Johnson & Johnson QA personnel and comments relating to the consistency of reporting were provided (b) (4) for their consideration before the final reports were issued. The final audit reports were reviewed by Johnson & Johnson clinical and regulatory staff for consistency. Amended reports involved only the upgrading of findings. All of the audit reports were finalized by Johnson & Johnson by November 6, 2009 and all addenda by November 30, 2009.

DSI Assessment of Response: Johnson & Johnson has adequately responded to this request. Note that across the 4 RECORD studies, 2.0-6.9% of sites were audited, with audits of 2.8-9.9% of total subjects in the studies. This will be taken in the context of audit findings as discussed below for each of the RECORD 4 studies.

iii. In addition to any other information within your audit report, address the following questions or requests:

- **At each site audited, how many violations involved each of the following specific issues? For each specific violation, list the clinical sites involved and provide a breakdown by treatment group for each site and overall for the four RECORD studies.**
  - **Enrollment of subjects that did not meet study eligibility criteria.**
  - **Failure of the Principal Investigator to ensure that all associates and colleagues assisting in the investigation were meeting the commitments of the study protocol.**
  - **Failure to report adverse events and serious adverse events**
  - **Failure to randomize subjects preoperatively**
  - **Failure to obtain informed consent from all subjects**
- **List all clinical sites where either Bayer or CRO monitoring is determined to be ineffective, either in identifying significant violations or in taking actions towards securing compliance (such as notifying the sponsor).**

Response to 1.c.iii.

J&J Analysis of (b) (4) Audits

Prior to submission of the complete set of (b) (4) audit reports, Johnson & Johnson submitted an analysis of the audits in a March 5, 2010 meeting background package. A brief summary of the Johnson & Johnson analysis is given here. Johnson & Johnson analyzed the (b) (4) audits using two approaches:

1. By six audit categories (informed consent, investigational product, SDV/CRF, safety, study conduct, monitoring).
2. By specific audit findings by classification category (critical, major, and minor).

Across the 30 audited sites, there were a total of 251 findings. Nineteen of these findings were categorized by (b) (4) auditors as critical, 121 were categorized as major and 111 were categorized as minor. The number of major findings per site ranged from 1 to a maximum of 10, with 12 of the 30 sites having 5 or more major findings (RECORD 1: 3/11 [27%], RECORD 2: 2/7 [29%], RECORD 3: 1/3 [33%], RECORD 4: 6/9 [67%]). The 19 critical findings recorded by (b) (4) occurred at 13 of the 30 audited sites in the following categories:

- 1 finding for Informed Consent
  - For one subject at one site, a signed consent form was not available.
- 2 findings for Investigational Product
  - Documentation of the Investigational Product administration during the inpatient phase of the study was either missing or insufficient.
- 6 findings for Source Data Verification and Case Report Form Completion
  - These critical findings can be further broken down into findings related to missing medical records (15 subjects at 4 sites), and significantly deficient and discrepant source documentation (2 sites).
- 4 findings for Safety
  - These findings were associated with adverse events that weren't reported and/or deficient safety reporting practices.
- 5 findings for Study Conduct
  - These can be further broken down into findings related to eligibility (9 subjects; 1 each at 2 sites, 7 at one site), protocol violations for study drug treatment outside the protocol specified time window (19 subjects at one site), and an improperly constituted ethics committee (1 site).
- 1 finding for Monitoring
  - The site monitor had failed to detect unreported adverse events, failed to detect late reporting for SAEs, and failed to meet with the principal investigator for 6 months, and failed to document training.

Further, Johnson & Johnson noted that there were a total of 603 audit identified (AI) AEs in the 931 audited subjects from 28 of 30 sites audited. The highest proportion of subjects with AI AEs were in the RECORD 4 study. There were eight AI SAEs found, all from RECORD 4 sites; five of these were newly reported events and three were upgraded AEs. Johnson & Johnson concluded the following regarding unreported AEs:

- Qualitatively, the most commonly reported AEs were similar in the audited subjects compared to those seen overall in the originally reported RECORD population.
- The AI-AEs appear to be balanced between the two treatment groups and their inclusion does not substantially alter the previously reported event rates in the audited subjects.

- RECORD 4 was found to have the largest number of AI-AEs, and all of the unreported SAEs were identified exclusively in the RECORD 4 study.
- Overall, the identification of the AI-AEs and AI-SAEs did not alter the previously reported safety profile of rivaroxaban.

The applicant notes that the efficacy endpoint in the RECORD studies was a hard composite endpoint of death, symptomatic VTE, or venographically detected VTE. They also note that the (b) (4) audits did not identify any evidence that would suggest that any of the venography data were not reliable; similarly, the audits did not identify any possibly missing or invalid symptomatic DVT or PE events. The sponsor concludes that the results of the RECORD studies are valid and reliable, but that the RECORD 4 study monitoring process should be specifically further addressed by a data validation plan, outlined in their submission.

DSI Assessment of Response: The sponsor's response is considered adequate to address the request in the CRL. In the following section, DSI will specifically analyze the (b) (4) Audits and will discuss the (b) (4) Audit findings considered critical to the evaluation of data reliability.

III. DSI Analysis of (b) (4) Audits

This section will provide DSI's analysis of the (b) (4) Audits focusing on items deemed critical to evaluations data reliability:

- Adequacy of Monitoring
- Human Subject Protections and Adverse Event Reporting
- Post-Operative Randomization
- Drug Accountability
- Eligibility

This section will also briefly touch upon (b) (4) Verification of RECORD 4 Data.

1. Adequacy of Monitoring

In one method used during the (b) (4) audits to assess adequacy of site monitoring, (b) (4) auditors reviewed each individual monitoring report. The Patient Data Check (PDC) Form was then completed for each subject, answering the question: "Was the monitoring effective, either in identifying significant violations or in taking actions towards securing compliance? The results are as follows (subjects inadequately monitored/subjects audited (%))

RECORD 1: 96/347 (27.2%)
RECORD 2: 55/216 (25.5%)
RECORD 3: 28/70 (40.0%)
RECORD 4: 197/312 (63.1%)

The (b) (4) audit reports note that inadequate monitoring was considered to be present at 2/11 (9%) of RECORD 1 sites, 2/7 (29%) of RECORD 2 sites, 1/3 (33%) of RECORD 3 sites, and 4/9 (44%) RECORD 4 sites (Table 4) according to (b) (4) assessment. Note that not all audit reports contained a specific statement regarding adequacy of monitoring. DSI review of the

audit reports yielded an additional RECORD 4 site at which (b) (4) monitoring did not detect findings which would affect the primary efficacy or safety outcome (Table 4). For 3 additional audit reports (2 at RECORD 1 sites and 1 at a RECORD 2 site), it could not be determined from review of the audit report whether key primary efficacy or safety issues detected by the (b) (4) auditors were noted by the Bayer/(b) (4) monitors. Key primary efficacy or safety issues included study drug administration inconsistencies between source documents and eCRF, drug accountability and dosing issues, identical drug dispensation times for all subjects, and inclusion of a subject with intraocular hemorrhage in violation of the exclusion criteria. Note that (b) (4) audits of many other sites demonstrated missed monitoring issues with respect to protocol deviations, adverse event reporting, source document verification, etc. However, only those instances in which monitoring omissions involved primary efficacy parameters or safety issues, which are considered critical for the evaluation of data integrity, are addressed here. In addition, instances where a single subject at a site had an issue impacting safety or efficacy are not included here since these instances would be unlikely to significantly impact overall site data reliability. Rather, review has focused on findings at sites where a substantial number of subjects were impacted at the site, such that overall data reliability of the site is in question. Please see Table 8 in Section III.5. for a listing of specific issues impacting on data reliability at individual sites.

Table 4: Monitoring Adequacy and Issues Based on (b) (4) Audit Reports

	RECORD 1	**RECORD 2**	**RECORD 3**	**RECORD 4***
# of (b) (4)-audited Sites with Monitoring Deficiencies (n)/Total # of sites audited by (b) (4) (N)	**Number sites (n/N; %)**	**Number sites (n/N; %)**	**Number sites (n/N;%)**	**Number sites (n/N;%)**
Per (b) (4) audit reports; DSI concurs	2/11 (9%)	2/7 (29%)	1/3 (33%)	4/9 (44%)
Monitors missed key primary efficacy or safety issue per DSI review of (b) (4) audit	0/11 (0%)	0/7 (0%)	0/3 (0%)	1/9 (11%)**

*(b) (4) was monitor

**Sepulveda (Site 32002): Monitoring did not detect study drug administration inconsistencies between source documents and eCRF.

The specific sites deemed by Johnson & Johnson analysis of the (b) (4) audits to have ineffective monitoring are the following:

Garces, RECORD 1, Site 240002: Monitoring was inadequate to detect some unreported AEs, medical historical information, and protocol deviations; 90% of subjects audited had a "no" response given for the PDC question.

Slappendel, RECORD 1, Site 30002: The Executive Summary of the audit states that monitoring is inadequate. 91% of subjects audited had a "no" response given for the PDC question.

Ono, RECORD 2, Site 50005: 92% of subjects audited had a "no" response given for the PDC question.

Wang, RECORD 2, Site 54001: Monitoring inadequate as judged by a significant number of eCRF versus source discrepancies; 46% of subjects audited had a "no" response given for the PDC question.

Brabants, RECORD 3, Site 28015: 100% of subjects audited had a "no" response given for the PDC question.

Kilgore, RECORD 4, Site 14034: 66% of subjects audited had a "no" response given for the PDC question.

Reddy, RECORD 4, Site 60001: Numerous protocol/GCP deviations were unreported by the monitor; 100% of subjects audited had a "no" response given for the PDC question.

V. Shah, RECORD 4, Site 60006: Numerous protocol/GCP deviations were unreported by the monitor; 100% of subjects audited had a "no" response given for the PDC question.

H. Shah, RECORD 4, Site 60004: Numerous protocol/GCP deviations were unreported by the monitor; 100% of subjects audited had a "no" response given for the PDC question.

Modi, RECORD 4, Site 60010: None of the issues noted in this report were noted as deviations by the monitor. 97% of subjects audited had a "no" response given for the PDC question.

It could not be determined from DSI evaluation of the (b) (4) audit results from Dr. Garces and Dr. Wang's sites whether inadequate monitoring of the site resulted in a deleterious effect on key primary efficacy and/or safety findings from those sites. However, review of the (b) (4) audit results themselves did not raise concerns as to data reliability of these sites.

Johnson & Johnson also submitted reports of 74 clinical investigator site audits conducted by Bayer GCP Study Audit Management for the RECORD 1-4 studies, 69 of which were routine. Review of the Bayer audit reports for the clinical investigator sites for which (b) (4) and/or DSI considered that the data was unreliable (when available) showed that in the majority of instances, the violation considered most significant by DSI was not reported in the Bayer audit report. Significant deficiencies at the sites of Drs. Lenart (RECORD 1), Porvaneckas (RECORD 1), Nararrete (RECORD 2), and Buettner (RECORD 4), described in the (b) (4) audit reports were not mentioned in the Bayer audit reports. Although significant findings were identified at Dr. Michael Murray's RECORD 4 site during the Bayer audit, the issues identified by FDA inspectors resulting in an OAI classification were not noted. The initial two Bayer audits at Dr. Craig Loucks site in RECORD 4 did not report forgery of the Principal Investigator's signature, which was subsequently reported to the IRB by a site CRA. Failure to identify via site audits these serious regulatory violations identifies adequacy of monitoring as a problem in the RECORD trials, especially RECORD 4.

DSI Assessment of Response:
Based on DSI review of (b) (4) audit reports, (b) (4) auditors stated that overall study monitoring was deficient at 1 of 11 (9%) sites in RECORD 1, 2 of 7 (29%) sites audited in RECORD 2, 1 of 3 (33%) sites audited in RECORD 3, and 4 of 9 (44%) sites audited in RECORD 4. DSI concurs that monitoring was deficient at these sites. According to DSI review, (b) (4) monitoring failed to detect a key efficacy or safety issue in one additional instance in RECORD 4 (Dr. Sepulveda). It could not be determined from DSI evaluation of the (b) (4) audit results from Dr. Garces and Dr. Wang's sites whether inadequate monitoring of the site resulted in a deleterious effect on key primary efficacy and/or safety findings from those sites. It should be noted that these findings impacted a substantial number of subjects at each site, such that overall data reliability of the sites is in question.

Review of the audit reports for RECORD 1, 2, 3, and 4 submitted by Johnson & Johnson also revealed that Bayer/ (b) (4) audits did not always identify serious deficiencies.

(b) (4) assessment of monitoring ineffectiveness by PDC forms showed that 63% of subjects in RECORD 4 audited were not monitored effectively. RECORD 1 and 2 had similar levels of unreliable monitoring, 27% and 29%, respectively. The relatively high level of ineffective monitoring (40%) noted in RECORD 3 is very likely reflective of the comparatively low number of subjects audited in RECORD 3 together with the presence of a problematic site (Brabants – see Section III.3. below) which enrolled 27 subjects.

The frequency of monitoring ineffectiveness was less in RECORD 1, 2, and 3 as compared to RECORD 4; however, there was not as large a difference between monitoring ineffectiveness between RECORD 3 as compared to RECORD 4. However, as noted above, this assessment ineffectiveness by (b) (4) was based solely on PDC form checks. Note that in DSI's assessment of monitoring adequacy of all 4 RECORD studies, assessment of monitoring effectiveness/ineffectiveness was not based solely on PDC form evaluation and respective percentages, but rather on the specific findings and their impact on data reliability. As such, perhaps from a percentage standpoint, it may be noted that monitoring ineffectiveness of 40% for RECORD 3 is not substantially different from the 63% monitoring ineffectiveness for RECORD 4 based on the PDC form check; however, taking into account not only PDC form checks, but also the extent and scope of deficiencies noted in RECORD 4, particular concerns are raised regarding data reliability of RECORD 4 based on evaluation of monitoring.

Overall, monitoring deficiencies were noted for all 4 RECORD studies; however, in comparison to RECORD 1-3, the extent and scope of monitoring deficiencies noted for RECORD 4 are considered more significant and raise concerns regarding pervasiveness of monitoring deficiencies for other sites not inspected or audited, and as such undermine the confidence in reliability of the data.

2. Human Subject Projection and Adverse Event Reporting in (b) (4) Audit Reports

Human Subject Protection

In Table 5 below are presented clinical investigator sites where any instance of failure to protect human subject rights was noted during DSI review of the (b) (4) audits. Data from the sites of Drs. Brabants, Mody, and V. Shah were assessed by DSI as unreliable based on efficacy findings as given in Table 8 in Section III.5. Additionally, four women of childbearing potential were enrolled in RECORD 2 without performance of a pregnancy test; omission of the pregnancy tests were intentional, based on cultural factors. This protocol violation had the potential to significantly adversely impact any pregnancies which had been preexisting to the study. Although the events documented at the sites of Drs. Bauer, Marinoni, and Field are of substantial concern to DSI, they either involve a single individual or did not result in subject harm, and as such are unlikely to impact data reliability of these 3 specific sites.

Table 5: Clinical Investigator Sites with Instances Where Subject Safety Was Not Protected Based on DSI Review of (b) (4) Audit Reports

Study	Clinical Investigator Site number Number of subjects	Detail
RECORD 1	Bauer Site 44003 63 subjects	One subject with untreated hypertension
RECORD1	Marinoni Site 22001 15 subjects	• Subject 4003 Subject had history of disturbed vision & ITP = exclusion criteria. Subject had "pre-retinal hemorrhage" Day 1, study medication continued. • 4 subjects had epidural catheters inserted or removed outside of protocol requirements; none of these catheters were recorded on the CRF. Two were placed too soon after study drug administration (1.5 and 2 hours) and 2 were withdrawn too soon after study drug administration (1.5 and 4 hours after dose, rather than 2X the half-life)
RECORD 2	Field Site 12008 140 subjects	Subject 7989-251107 had a diagnosis of chronic renal insufficiency (CRI) per medical records, no screening labs reviewed prior to surgery (b) (6), screening labs signed by PI 10/14/06, subject withdrawn due to elevated BUN/Cr on 10/13/06.
RECORD 2	Wang Site 54001 88 subjects	Four of six women of child bearing potential did not have pregnancy test performed prior to enrollment in the trial
RECORD 3	Brabants Site 28015 27 subjects	9 of 27 subjects had screening procedures performed prior to signing Informed Consent
RECORD 4	Mody Site 60010 68 subjects	• Ethics Committee (EC) impartiality could not be confirmed, as the EC was established at the PI's request, and the members had no training or prior experience. • Clinician review of study documents (laboratory studies, ECGs) for 25/35 subjects (71%) was either not done or not done in a timely fashion. Example = ECG showing anterior wall myocardial ischemia.
RECORD 4	V. Shah	Language used to discuss the Informed Consent

Site 60006 80 subjects	document with all subjects was coercive, with documentation indicating that he said "that the study drug was completely safe, that it is the best treatment currently available, that risks were minimal (same as any other surgery). . ."

Adverse Event Reporting

The (b) (4) audit reports were reviewed in order to assess the adequacy of adverse event reporting. Only 2 of the 30 audited sites had no unreported adverse events identified during the audits. The number of unreported adverse events ranged from 1 to 54 per site. Eight unreported SAEs were identified, all at RECORD 4 sites. Unreported adverse events were assessed as "significant" by the DSI reviewer if they clearly required further expeditious medical evaluation; all events which included bleeding or elevation of liver function tests were included in this category. Anemia in itself was not considered "significant".

Table 6 below summarizes unreported AEs by clinical investigator site audited by (b) (4).

Table 6: Unreported Adverse Events

RECORD study	Investigator	Number and type of unreported SAEs	Number of unreported adverse events/number of subjects with unreported adverse events (Excludes SAEs)	Number of unreported adverse events of significance – clearly required medical evaluation	Examples of significant unreported adverse events
RECORD 1	Bauer	0	4/4	1	GGT = 205
RECORD 1	Kruczynski	0	1/1	0	-
RECORD 1	Lenart	0	1/1	0	-
RECORD 1	Marinoni	0	5/4	1	Abnormal ECG
RECORD 1	Mazurkiewicz	0	4/4	0	-
RECORD 1	Garces	0	8/6	1	Disorientation
RECORD 1	Pesola	0	2/2	0	-
RECORD 1	Porvaneckas	0	22/12	3	Allergic skin reaction, elevated BP
RECORD 1	Schwartsmann	0	0	0	-
RECORD 1	Slappendel	0	54/21	9	SOB, wound hematoma, calf red/painful, fever, low HR requiring Rx
RECORD 1	Stehlik	0	12/11	1	Hypotension and chest pain
RECORD 2	Belickas	0	8/7	2	Fever
RECORD 2	Dhanjee	0	4/4	3	Hypotension, calf pain, fever
RECORD 2	Field	0	21/13	2	Leg swelling elevated GGT
RECORD 2	Martson	0	9/5	3	Thigh hematoma, fever, hypotension
RECORD 2	Nafarrete	0	34/10	4	Infection
RECORD 2	Ono	0	37/16	7	Hypertension, nasal

Table 6: Unreported Adverse Events

RECORD study	Investigator	Number and type of unreported SAEs	Number of unreported adverse events/number of subjects with unreported adverse events (Excludes SAEs)	Number of unreported adverse events of significance – clearly required medical evaluation	Examples of significant unreported adverse events
					bleeding during surgery
RECORD 2	Wang	0	18/14	3	Hypertension, dyspnea
RECORD 3	Brabants	0	36/20	2+*	Leg hematoma;
RECORD 3	Paulsson	0	1/1	0	-
RECORD 3	Synder	0	0	0	-
RECORD 4	Dessouki	1: cholecystitis/ cholecystectomy	18/15	14	Shaking with fever & hallucinations, drug-induced pancreatitis, elevated GGT = 275, ARI, decreased platelets, Na = 119 with K = 2.5, irregular HR, Tx 2U PRBCs, burning calf
RECORD 4	Hollman	0	7/6	0	-
RECORD 4	Jove	0	33/13	7	Fever, hypotension, UTI
RECORD 4	Kilgore	1: Respiratory failure	29/25	3	SOB, Elevated AST/ALT/GGT/alk phos
RECORD 4	Mody	3: Chest infection requiring hospitalization; bedsore requiring hospitalization; hypotension & SOB requiring transfer.	47/21	7	Chest pain/breathing difficulties, Tx 2U PRBCs, fever, hypertension, amylase
RECORD 4	Reddy	3: Grade II adenoCA of the prostate; pyrexia requiring hospitalization; hospitalization more than 12 hours for catheterization	38/10	10	Fever, elevated bilirubin, left bundle branch block, decreased platelets, elevated ALT
RECORD 4	Sepulveda	0	13/25	8	Edema, hematoma, wound infection,

Table 6: Unreported Adverse Events

RECORD study	Investigator	Number and type of unreported SAEs	Number of unreported adverse events/number of subjects with unreported adverse events (Excludes SAEs)	Number of unreported adverse events of significance – clearly required medical evaluation	Examples of significant unreported adverse events
RECORD 4	H. Shah	0	44/19	7	ALT/AST > 3X ULN Probable LVH, possible MI, pitting edema, neutropenia, irregular heart beat
RECORD 4	V. Shah	0	36/17	5	Fever, LE swelling, elevated ALT > 3X ULN

*Many are unspecified abnormal hematology and chemistry values

The total number of unreported adverse events for each RECORD study is as follows:

RECORD 1 – 110; 16 significant*
RECORD 2 – 131; 24 significant
RECORD 3 – 37; 2+ significant
RECORD 4 – 265; 61 significant
Total RECORD studies – 543; 103+ significant
*see note below in "DSI Assessment of Response" as to how "significant" was defined

Although slightly more RECORD 4 subjects were audited than in other 3 studies (and RECORD 3 subjects were audited less frequently), it appears that RECORD 4 has a disproportionate number of unreported adverse events as well as unreported significant adverse events when compared with the other RECORD studies. In addition, RECORD 4 was the only study with unreported SAEs.

DSI Assessment:
(b) (4) audit reports of two clinical investigator sites of 11 audited for RECORD 1 (Drs. Bauer and Marinoni), 2 sites of 7 audited for RECORD 2 (Mr. Field and Dr. Wang), 1 site of 3 audited for RECORD 3 (Dr Brabants), and 2 sites of 9 audited for RECORD 4 (Drs. Mody and V. Shah) demonstrated instances where human subject rights were not protected during the conduct of the RECORD studies. However, the findings noted in Tables 5 and 6 above for Drs. Bauer, Marinoni, Field and Wang, are not considered pervasive in nature, and unlikely to impact data reliability for their respective RECORD 1-3 studies. The findings for Drs. Mody and Shah are concerning and provide further evidence for the distinction between study monitoring/conduct of RECORD 4 as compared to RECORD 1-3.

(b) (4) audits of the majority of sites identified unreported adverse events, ranging from 0 (2 sites) to 54 per site. When adverse events considered significant by DSI (defined as adverse events which clearly required expeditious medical evaluation and all events including bleeding or elevation of LFTs), there were 16 significant unreported AEs in RECORD 1, 24 in RECORD 2, 2+ in RECORD 3 (exact number could not be determined), and 61 in RECORD 4. Unreported AEs and SAEs identified during the data verification process conducted by (b) (4) will be presented in Section III. 6.

The finding of unreported adverse events during the (b) (4) audits did not alone result in a DSI determination that data from these sites were unreliable. However, the striking finding on examination of the number of unreported adverse events and SAEs per study is the disproportionate number of adverse events detected during the (b) (4) audits of RECORD 4 (more than twice the number of undetected AEs and significant AEs) when compared with the smaller numbers reported from RECORD 1, 2, and 3. Of additional concern, are the eight unreported SAEs noted by (b) (4) auditors from the RECORD 4 audits, whereas no undetected SAEs were reported from RECORD 1, 2, or 3. The disproportionate number of adverse events detected during the (b) (4) audits of RECORD 4 when compared with RECORD 1, 2, and 3, as well as the detection of unreported SAEs only in RECORD 4 brings into question the adequacy and completeness of the RECORD 4 safety data submitted to the Agency. In addition, the relatively large number of unreported adverse events raises further concern regarding the adequacy of study conduct and monitoring of RECORD 4.

3. Post-operative Randomization in (b) (4) Audit Reports

As noted in Table 2, post-operative randomization was identified by FDA audits for the NDA submission at 3 clinical investigator sites (Drs. Murray, Ward, and Buettner), all enrolling in RECORD 4, in violation of the protocol. This is despite the fact that (b) (4) the CRO monitoring RECORD 4, sent an email to all sites during the clinical trial reiterating the protocol requirement that subjects be randomized prior to surgery. One FDA inspection noted that the investigator gave permission to randomize after the patient stopped oozing at the surgical wound site.

As part of the CR, Johnson & Johnson determined the incidence of postoperative randomization at all RECORD sites. The results are as follows:

Postoperative randomization was assessed in most RECORD 4 (b) (4) audit reports with the following specific information regarding post-operative randomization (number of subjects randomized postoperatively/total subjects enrolled in study (%)):

RECORD 1: 18/4541 (0.4%)
RECORD 2: 13/2509 (0.5%)
RECORD 3: 9/2531 (0.4%)
RECORD 4: 1227/3148 (39.0%)

Dessouki - 18/35 randomized day of surgery, no time stamp on IVRS form
Hollman - Two subjects randomized post-operatively
Jove - No subjects randomized post-operatively

Kilgore - "Majority" of subjects randomized day of surgery, no time stamp on IVRS form
Mody - 34/35 subjects randomized day of surgery, no time stamp on IVRS form
Reddy - 12/40 subjects randomized post-operatively, deviation forms on file for 11 of these 12 subjects, in 7/40 subjects the time of randomization couldn't be determined
Sepulveda - 9 subjects were randomized on the day of surgery, no time stamp on IVRS form; there was no randomization sheet available for 1 subject
H. Shah - 1 post-operative randomization
V. Shah – no subjects noted to be randomized post-operatively

Based on these results, there are three RECORD 4 clinical investigator sites from the (b) (4) audits where subjects were randomized postoperatively (Drs. Hollman, Reddy, and H. Shah; at Dr. Reddy's site, these events were identified as protocol violations). At four additional sites (Dr. Dessouke, Kilgore, Mody and Dr. Sepulveda), it cannot be determined from the information available in the (b) (4) audit reports what proportion of the subjects were randomized postoperatively. Therefore, based on the (b) (4) audit reports, post-operative randomization occurred at a significant number of clinical investigator sites enrolling in RECORD 4. This protocol violation occurred in 3 of 5 of the sites originally inspected for the NDA, and to varying degrees in 3 additional sites audited by (b) (4) in addition, it cannot be determined from the site records whether subjects randomized on the day of surgery were in fact randomized post-operatively.

DSI Assessment of Response

According to Johnson and Johnson, postoperative randomization took place for 1227 of 3148 (39%) of RECORD 4 subjects, audited and nonaudited by (b) (4) Based on the (b) (4) audit results, 3 of the 9 sites audited for RECORD 4 randomized postoperatively; at 4 additional sites, it cannot be determined from the information available in the (b) (4) audit reports what proportion of the subjects randomized on the day of surgery were in fact randomized post-operatively. Although such postoperative randomization errors would occur in both arms of the clinical trial, it has the potential to alter the patient population included in the RECORD 4 study. If sufficient sites enrolled subjects postoperatively, especially based on specific criteria, the population included in the Xarelto product label may not reflect the population actually studied. The review division will need to assess the impact of this issue on potential product labeling. The high incidence of this protocol violation again reinforces the monitoring deficiencies in RECORD 4. Although (b) (4) was aware of the occurrence of postoperative randomization, they did not effectively enforce compliance with this protocol requirement. Post operative randomization did not occur to any significant degree in RECORD 1, 2, or 3.

4. Drug Accountability Issues in (b) (4) Audits

Review of the (b) (4) audit reports focused on identification of clinical investigator sites where there were documentation issues for study drug administration and/or storage. Attention was focused on identified problems with drug administration of accountability and/or administration, such that uncertainty existed as to whether subjects actually received the assigned study drug which had been stored appropriately to maintain activity. If subjects did not receive study drug as described in the data listings, the primary efficacy outcome could potentially be compromised.

DSI concurs with (b) (4) assessment of data from Dr. Brabants site (RECORD 3) as unreliable due to inadequacies in study drug administration documentation. Based on a review of the (b) (4) audit reports, DSI identified four additional sites for RECORD 1 (Drs. Lenart, Porvaneckas, Schwartsmann, and Slappendel), two additional sites for RECORD 2 (Drs. Naraffete and Ono), and three additional sites for RECORD 4 (Drs. Mody, Sepulveda, and Shah) which have sufficient deficits in drug administration and accountability that DSI cannot verify subjects received study drug as purported. Details of drug accountability issues for each CI are given in Table 7. At each of the additional sites, source documentation for study drug administration was missing or lacking, and/or there were significant issues with documentation of drug accountability such that it does not appear possible to verify that subjects at the site received active/correct study drug therapy.

Table 7: Clinical Investigator Sites with Drug Administration and Accountability Issues Based on (b) (4) Audits

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Major Drug Accountability/Administration Issues
Robert Slappendel Netherlands	RECORD 1 Site 30002 61 subjects	DSI review of (b) (4) site audits	• No source documentation for date/time of the pre-operative self-administered injection of enoxaparin/placebo by the subject or the date and time of last outpatient dosing • 10 of 35 subjects audited had drug accountability records which were incomplete and/or discrepant with other subject source documentation.
Endre Lenart Hungary	RECORD 1 Site 46002 87 subjects	DSI review of (b) (4) audit reports	Study coordinators log used to document drug accountability and dosing for all subjects, but entries in log were not dated/initialed
Narunas Porvaneckas, Lithuania	RECORD 1 Site 57001 72 subjects	DSI review of (b) (4) audit reports	Study drug administration times were exactly the same for all 34 subjects audited. Exact dosing times were not documented.
Edmundo Berumen Naraffete	RECORD 2 Site 32005 25 subjects	FDA review of (b) (4) site audits	Study drug administration times were exactly the same for each subject for all subjects audited
Keiske Ono Brazil	RECORD 2 Site 50005 24 subjects	FDA review of (b) (4) site audits	• Documentation of study drug administration during inpatient phase of study was missing or deficient: 8 subjects records contained

			very few notations that study drug had been given, and the remaining 16 records contained none. Doses documented on the SDW were not signed/initialed or dated • Large number of discrepancies between eCRF, SDW, and medical chart information (73 discrepancies for 20 subjects – e.g. surgery start/stop time, intraoperative blood loss, drain volume)
Karl Brabants Belgium	RECORD 3 Site 28015 27 subjects	(b) (4) site audits	• Exact time of study drug administration was rarely recorded on the inpatient medication administration records for any of the 27 subjects – only on grid with 0800, 1200, 1600, and 2000 time points • Times of study drug administration frequently do not match the times noted on the inpatient medication administration sheets • Study coordinator was unable to define a consistent primary source for many of the data points, including drug dosing, surgery start/stop times, and laboratory draw times. • Drug accountability logs provided by Bayer were not used by the study coordinator to record drug accountability and the site did not keep a log of accountability • Ambient temperatures in study drug storage room was monitored weekly, not daily
Bharat Mody India	RECORD 4 Site 60010 68 subjects	FDA review of (b) (4) site audit	Study drug not stored in permissible temperature range of 15-30^{o}C for 19 consecutive days, dropping to 10.2^{o}C each day
Victor Sepulveda Mexico	RECORD 4 Site 32002	FDA review of (b) (4) site audit	• Medical records of 10 subjects were missing from

	46 subjects		the site. Nursing notes, which include dosing entries, were missing for an additional 7 subjects • 15 of 33 subjects audited had source vs eCRF discrepancies pertaining to study drug administration noted (ranging from 1 to all doses, most = 2-3 doses)
V. Shah India	RECORD 4 Site 60006 80 subjects	DSI review of (b) (4) site audit	• Data discrepancies exits between the eCRF and site source documentation, including for study drug administration (26 subjects, 23 instances) • Missing source documentation of drug administration for 8 of 35 subjects[c]

Further information was requested by the FDA on August 2, 2010 regarding the (b) (4) audit findings at eight clinical sites (sites with significant drug accountability issues as identified in Table 7 above). This Information Request was intended to obtain any additional information which might be available at the clinical sites to clarify what the (b) (4) auditors considered to be inadequate drug accountability. Please see Appendix 2 for details of DSI requests, response/finding from Johnson & Johnson received on September 26, 2010, and DSI assessment of the additional information provided. Johnson & Johnson sent monitoring personnel to seven of the clinical sites in question; the entire team including Dr. Slappendel and the Study Coordinator is no longer present at his site, so the RECORD 1 study team attempted to provide additional clarification. The results of the site revisit to Dr. Schwartsmann's site provided sufficient evidence that study drug was given appropriately. However, the data provided for the other sites was insufficient to provide such reassurance.

DSI Assessment of Response

In conclusion, issues in drug accountability were identified across the RECORD studies, most seriously in RECORD 4. In some instances, it appears that routine hospital practice was followed (e.g., physician notes what time medication should be given and this information is copied onto a nurse's sheet, with initials/dates/times of drug administration recorded only if there were variations from this procedure). However, for purposes of a clinical trial, it is imperative that documentation sufficient to assure that medication was actually administered to study subjects be provided in the source documents. The absence of actual dates/times of drug administration as well as initials of the person administering the medication results in an inability to have confidence that the subject actually received the medication as specified in the protocol.

Overall, there were some drug accountability issues identified by (b) (4) audits at sites from all of the RECORD studies. The statistical import of the single site in RECORD 3 identified with

significant drug accountability issues is difficult to assess, given that only 3 sites were audited from RECORD 3. We acknowledge that RECORD 1 had 3 sites with significant drug accountability issues, and RECORD 2 had 2 sites. These findings for RECORD 1 and 2, when interpreted together with the failure to identify deficiencies in drug accountability in FDA inspection and the relatively small number of sites audited, do not allow extrapolation to the conclusion that all sites from RECORD 1 and 2 had drug accountability deficiencies sufficient to impugn data integrity from all sites in these studies. The ultimate decision regarding overall study reliability must be based on the totality of evidence pertinent to good clinical trial conduct. In contrast to RECORD 1, 2, and 3, however, RECORD 4 had 3 sites identified with significant drug accountability issues by (b) (4) audit, in addition to the 2 RECORD 4 sites (Cources and Esquivel) already identified by DSI as unreliable based on drug accountability issues, among other violations. This suggests that drug accountability deficits are more pervasive at RECORD 4 sites. Please see Section IV. Below for a further discussion of the effect of drug accountability on overall study data reliability.

5. Eligibility Criteria in the (b) (4) Audits

One item of concern identified during the initial cycle of FDA inspections was enrollment of subjects in violation of the protocol inclusion criteria. Review of the (b) (4) audit reports revealed a few subjects enrolled who did not meet eligibility criteria, but this was not a frequent finding.

DSI Assessment of Response
Enrollment of ineligible subjects does not appear to be a systematic problem in the RECORD studies.

6. (b) (4) Verification of RECORD 4 Data

As described in Section C.1. above, deficiencies in monitoring by (b) (4) and study conduct issues appeared to be more severe and widespread in the RECORD 4 study when compared with the RECORD 1, 2, and 3 studies. Therefore, the applicant proposed a data verification plan in an attempt to demonstrate the validity of the RECORD 4 data. The sponsor's plan was presented to the Division of Hematology Products and DSI on April 7, 2010. The goal of the data verification was to identify any AEs or SAEs present in the subjects' medical records that were not reported to Bayer before the time of finalization of the study, to assess overall site and investigator quality, to assess the impact of postoperative randomization, and to address the Agency's areas of concern regarding study reliability. All sites participating in RECORD 4 were to be visited by site monitors from (b) (4), an independent CRO. Please see the CR document dated December 23, 2010 for details of the data verification plan.

After revisiting all RECORD 4 sites, there were 260 newly identified treatment emergent adverse events in the rivaroxaban arm and 244 in the enoxaparin arm. This resulted in an increase in the reported rate of adverse events from approximately 80% of subjects originally reported with adverse events to 97% of subjects following data verification; there was no change in the distribution of AEs between treatment groups. There were 28 newly reported SAEs in 25 subjects (15 rivaroxaban, 12 enoxaparin, and 1 never randomized). There were 2

newly-reported cases of ALT>3X ULN concurrent with a total bilirubin >2X ULN identified, both in subjects receiving enoxaparin. No new events of death, DVT, or PE were identified.

(b) (4) monitors were instructed to answer a series of questions regarding site and investigator overall performance. Sites and investigators were then ranked according to quality. Sensitivity analyses were performed for primary efficacy and safety by high versus low quality sites/investigators. This procedure was intended to address site performance concerns raised by the agency. Based on this procedure, the sponsor concludes that the primary efficacy and safety results remained essentially unchanged in the groups of sites with performance considered by (b) (4) as acceptable or questionable, compared to that seen in the overall patient population.

In order to address the issue of postsurgical randomization, (b) (4) compared outcomes in subjects treated preoperatively versus postoperatively in both treatment arms. The applicant states that their results demonstrate that when the rates of the efficacy and safety outcomes were calculated in the two treatment groups for subjects randomized preoperatively versus postoperatively, they appeared to be comparable and similar to those results seen overall.

DSI Assessment of Response

The (b) (4) data verification audits of the RECORD 4 study sites were conducted with the intention of reassuring the Agency of the robust nature of the RECORD 4 data. The identification of 504 new treatment emergent adverse events as well as 28 newly identified SAEs in the RECORD 4 study provokes more concern than reassurance. Although it is certainly possible that there are unreported adverse events and SAEs in clinical trials in general, the number of unreported adverse events in the RECORD 4 trial seems excessive. Additionally, these newly reported adverse events reaffirm the concern that monitoring of the RECORD 4 trial was inadequate. Similarly, it is reassuring that no difference in efficacy or safety outcome was noted in subjects randomized pre- versus postoperatively. However, the large number of subjects randomized postoperatively in violation of the protocol raises again the issue of adequacy of study monitoring. The portion of the data verification process in which (b) (4) assessed site and investigator overall performance which was then correlated with efficacy and safety outcome is interesting, but not a validated method of assessing study conduct. DSI remains concerned with the deficiencies in clinical trial conduct and monitoring of RECORD 4 with potential deleterious effects on the validity of the efficacy and safety data from the RECORD 4 study.

IV. DSI Review of (b) (4) Audits – Unreliable Sites

In order to assess whether or not the findings from the (b) (4) audits significantly impacted overall data reliability from each CI site, DSI reviewed the 30 audit reports in detail. At many sites, (b) (4) auditors identified issues with study conduct, unreported adverse events, drug disposition and accountability, informed consent, source document verification and case report completion, and monitoring. If findings at a site involved more than a few subjects or appeared to significantly impact key efficacy assessments for multiple subjects, then DSI considered data from the site to be unreliable. Please see Table 8 for details of sites with efficacy data considered unreliable by DSI, which is based on review of the totality of information available to DSI, to include Bayer audits, (b) (4) audits, as well as FDA

inspections. The identification by (b) (4) monitors that adverse events had not been fully reported did not in and of itself result in site assessment as unreliable, especially if the balance of the issues rendered the site data assessment as reliable.

As seen in Table 8 below, data from the following clinical investigators had been previously identified based on DSI review of FDA inspections as unreliable with the recommendation that it should not be used in support of the application: RECORD 2: Drs. Corces and Yang; and RECORD 4: Drs. Loucks, Esquivel, Murray, Ward, and Buettner. DSI concurs with Falcon's assessment of data from Dr. Brabants site (RECORD 3) as unreliable, and this data should not be used in support of the application. Based on a review of the (b) (4) audit reports, DSI identified three additional sites for RECORD 1 (Drs. Lenart, Porvaneckas, and Slappendel), two additional sites for RECORD 2 (Drs. Naraffete and Ono), and three additional sites for RECORD 4 (Drs. Mody, Sepulveda, and Shah), which in DSI's opinion, provided unreliable data, and this data should not be used in support of the application. Note that the Executive Summary contained in the (b) (4) audit reports for each of these investigators lists multiple issues identified at each of these 8 sites, but stops short of stating that the data are unreliable. Only the data from Dr. Brabants' site was classified as unreliable by the (b) (4) auditors. At each of the additional sites, source documentation for key efficacy assessments was missing or lacking, and/or there were significant issues with documentation of drug accountability such that it does not appear possible to verify that subjects at the site received active/correct study drug therapy. The following table summarizes the reasons DSI recommends that data from individual CI sites be considered unreliable and not be used in support of the NDA. The source of the recommendation is also given as FDA inspection, (b) (4) audit report, or DSI review of (b) (4) audit report.

Table 8: Clinical Investigator Sites with Efficacy Data Considered Unreliable by DSI

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Primary Reason DSI Assesses Data from Site to be Unreliable
Endre Lenart Hungary	RECORD 1 Site 46002 87 subjects	DSI review of (b) (4) audit reports	Study coordinators log used to document drug accountability and dosing for all subjects, but entries in log were not dated/initialed, and as such can't verify accuracy of subject dosing.
Narunas Porvaneckas, Lithuania	RECORD 1 Site 57001 72 subjects	DSI review of (b) (4) audit reports	Study drug administration times were exactly the same for all 34 subjects audited. Exact dosing times were not documented, As such, can't verify accuracy of subject dosing.
Robert Slappendel[a] Netherlands	RECORD 1 Site 30002 61 subjects	DSI review of (b) (4) site audits	• No source documentation for date/time of the pre-operative self-administered injection of enoxaparin/placebo by the subject or the date and time of last outpatient dosing • 10 of 35 subjects audited had

Table 8: Clinical Investigator Sites with Efficacy Data Considered Unreliable by DSI

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Primary Reason DSI Assesses Data from Site to be Unreliable
			drug accountability records which were incomplete and/or discrepant with other subject source documentation[b]. As such, can't verify accuracy of subject dosing.
Arturo Corces Miami, U.S.A.	RECORD 2 Site 14012 19 subjects	FDA inspection	Recordkeeping and drug disposition deficiencies, considered significant enough to raise concerns regarding data reliability.
Qingming Yang China	RECORD 2 Site 54005 34 subjects	FDA inspection	Failure to report AEs, significant for evaluation of safety data as well as human subject protection
Edmundo Berumen Naraffete	RECORD 2 Site 32005 25 subjects	FDA review of (b) (4) site audits	Study drug administration times were exactly the same for each subject for all subjects audited; as such, can't verify accuracy of subject dosing.
Keiske Ono Brazil	RECORD 2 Site 50005 24 subjects	FDA review of (b) (4) site audits	• Documentation of study drug administration during inpatient phase of study was missing or deficient: 8 subjects records contained very few notations that study drug had been given, and the remaining 16 records contained none. Doses documented on the SDW were not signed/initialed or dated • Large number of discrepancies between eCRF, SDW, and medical chart information (73 discrepancies for 20 subjects – e.g. surgery start/stop time, intraoperative blood loss, drain volume) The findings raised significant concerns with respect subject dosing as well as adequacy and accuracy of data on CRFs, of significant concern to impact data reliability.
Karl Brabants Belgium	RECORD 3 Site 28015 27 subjects	(b) (4) site audits	• Exact time of study drug administration was rarely recorded on the inpatient medication administration records for any of the 27 subjects – only on grid with 0800, 1200, 1600, and 2000 time points • Times of study drug administration frequently do not

Table 8: Clinical Investigator Sites with Efficacy Data Considered Unreliable by DSI

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Primary Reason DSI Assesses Data from Site to be Unreliable
			match the times noted on the inpatient medication administration sheets • Study coordinator was unable to define a consistent primary source for many of the data points, including drug dosing, surgery start/stop times, and laboratory draw times. • Drug accountability logs provided by Bayer were not used by the study coordinator to record drug accountability and the site did not keep a log of accountability • Ambient temperatures in study drug storage room was monitored weekly, not daily
David Loucks Colorado, U.S.A.	RECORD 4 Site 14029 94 subjects	FDA inspection	• Recordkeeping deficiencies • Falsification • Protocol violations
Ricardo Esquivel Mexico	RECORD 4 Site 32006 42 subjects	Bayer monitoring	• Drug disposition record deficiencies • Missing records
R. Michael Murray Alabama, U.S.A.	RECORD 4 Site 14005 152 subjects	FDA inspection	• Post-operative randomization • Possible unblinding
John Ward Alabama, U.S.A.	RECORD 4 Site 14010 203 subjects	FDA inspection	• Post-operative randomization • Study continued despite lapse of IRB approval
Craig Buettner Alabama, U.S.A.	RECORD 4 Site 14004 61 subjects	FDA inspection	Post-operative randomization
Bharat Mody India	RECORD 4 Site 60010 68 subjects	FDA review of (b) (4) site audit	Study drug not stored in permissible temperature range of 15-30^{o}C for 19 consecutive days, dropping to 10.2^{o}C each day
Victor Sepulveda Mexico	RECORD 4 Site 32002 46 subjects	FDA review of (b) (4) site audit	• Medical records of 10 subjects were missing from the site. Nursing notes, which include dosing entries, were missing for an additional 7 subjects • 15 of 33 subjects audited had source vs eCRF discrepancies pertaining to study drug administration noted (ranging from 1 to all doses, most = 2-3

Table 8: Clinical Investigator Sites with Efficacy Data Considered Unreliable by DSI

Clinical Investigator Location	Study Site Number Number of Subjects	Assessment Source (FDA Inspections, (b) (4) Audit Reports, DSI Review of (b) (4) Audit Reports)	Primary Reason DSI Assesses Data from Site to be Unreliable
			doses)
V. Shah[b] India	RECORD 4 Site 60006 80 subjects	DSI review of (b) (4) site audit	• Data discrepancies exits between the eCRF and site source documentation, including for study drug administration (26 subjects, 23 instances) • Missing source documentation of drug administration for 8 of 35 subjects[c] • Use of inappropriate correction techniques in all subject records • For 3 subjects, source documentation and eCRF entries were changed months after an event, sometimes in response to a query from data management. • Language used to discuss the Informed Consent document with all subjects was coercive, with documentation indicating that he said "that the study drug was completely safe, that is the best treatment currently available, that risks were minimal (same as any other surgery). . ."

[a] Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from 4 of the 10 subjects in question at this site as acceptable; see Section III and Appendix 2; however, the data overall from this site is still considered unacceptable.
[b] Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from 1 of the 8 subjects in question at this site as acceptable; see Section III and Appendix 2; however, the data overall from this site is still considered unacceptable.

DSI Assessment of Response:
In addition to sites previously identified, based on DSI inspections as providing unreliable data with the recommendation that data from the sites not be used in support of the NDA (Drs. Corces and Yang for RECORD 2, and Drs. Loucks, Esquivel, Murray, Ward, and Buettner for RECORD 4), DSI concurs with (b) (4) auditors that data from Dr. Brabants' site enrolling in RECORD 3 be considered unreliable and that it not be used in support of the NDA. This recommendation is based on deficiencies in documentation of drug administration, such that certainty regarding study drug administration is not possible.

Based on review of the (b) (4) audit reports, DSI identified 3 additional sites for RECORD 1 (Drs. Lenart, Porvaneckas, and Slappendel), 2 additional sites for RECORD 2 (Drs. Naraffete and Ono), and 3 additional sites for RECORD 4 (Drs. Mody, Sepulveda, and V. Shah) from which DSI considers key study data to be unverifiable or unreliable and recommends that data

from these sites also not be used in support of the application. At each of these additional sites, source documentation was missing and/or there were significant issues with documentation of drug accountability such that it does not appear possible to verify that subjects at the site received active/correct study drug therapy.

As such data is not recommended for use from the following sites for their respective studies:
RECORD 1: Drs. Lenart, Porvanceckas, and Slappendal
RECORD 2: Drs. Coreces, Yang, Naraffete, and Ono
RECORD 3: Brabants
RECORD 4: Drs. Loucks, Esquivel, Murray, Ward, Buettner, Mody, Sepulveda, and Shah

DSI's assessment of how the inspectional/(b) (4) audit findings impact data reliability as a whole to each individual study based on the information available to DSI for review, is discussed in the next section.

V. DSI Overall Assessment of RECORD 1, 2, 3, and 4 Studies Based on (b) (4) Audits and FDA inspections

Inadequacies of study conduct and monitoring identified in the RECORD 1, 2, 3, and 4 studies during the initial NDA review cycle resulted in the request by DSI for independent third party audits of clinical investigator sites, which were conducted by (b) (4) Table 9 below summarizes the issues identified during FDA inspections and the (b) (4) audits which are considerations in the assessment of the overall integrity of each RECORD study.

Clearly, drug accountability issues at a significant number of sites in each RECORD study raises the fundamental issue of whether DSI is able (based on inspectional findings and (b) (4) audit results) to confirm that subjects at each site received study drug as given in the line listings submitted with the NDA. It can be seen in Table 9 that significant drug accountability issues (i.e. affecting more than a few subjects) were noted all 4 RECORD studies, ranging from 27 – 33% of (b) (4) audited sites. Since only three RECORD 3 sites were audited, the statistical significance of this finding for RECORD 3 is uncertain. In consideration of the potential impact of drug accountability issues on overall study data integrity, DSI evaluated other determinants of study reliability. A major determinant which enables DSI to generalize the results of audit or inspectional findings is adequacy of clinical trial monitoring. If monitoring is inadequate at the majority of sites examined, it becomes impossible for DSI to provide assurance that study conduct flaws (e.g., in drug accountability) did not occur at the vast majority of clinical sites which were not audited or inspected – or that other, undetected flaws impacting on safety and efficacy data did not occur. The same principle holds true for assessment of the number of sites assessed as unreliable after (b) (4) audit or FDA inspection. Given the relatively small percentage of subjects and sites examined, consideration must be given to interrelated study conduct issues (e.g., number of unreliable sites together with ineffective monitoring in a given study) – that is, the more essential elements of good study conduct that are defective in a given study, the more likely that overall data integrity for that study is unreliable. Lastly, DSI considered the relative number of unreported adverse events and serious adverse events in the assessment of overall study integrity. Although each RECORD study had flaws which had the potential to affect data integrity, DSI took a global

approach in applying analysis of each study conduct element to overall RECORD study reliability. We are of the opinion that assessment of significant site inadequacies in a given study across all examined study conduct issues allows a more accurate assessment of the impact of these issues on data integrity. Findings of deficits in a single area of study conduct makes extrapolation of assessment of data integrity as unreliable, problematic across an entire study, given the relatively small proportion of sites assessed. It seems reasonable, however, to have a higher level of confidence in drawing a conclusion that data integrity is unreliable, based on a small audit/inspectional sample for a given study, when all study conduct elements examined are significantly flawed. Please see discussion after Table 9 for application of these concepts to each RECORD study.

TABLE 9: EVALUATION OF RECORD 1, 2, 3, AND 4 DATA INTEGRITY

Study	Post-operative Randomization #subjects POR/total subjects (%)	Unreported Adverse Events – (b) (4) audits AEs/ significant AEs/SAEs	Unreported Adverse Events – (b) (4) audits AEs/ SAEs	Drug accountability issues (critical) Sites with issues/sites audited by (b) (4)	Inadequate monitoring (b) (4) overall assessment by subject assayed	Inadequate monitoring (b) (4) overall assessment by site assayed (sites with inadequate monitoring/sites audited) (%)	#sites unreliable (Sites unreliable/total sites audited by (b) (4) +FDA inspected)	Overall study reliability
RECORD 1 (217 sites)	18/4541 (0.4%)	110/16/0	NA	3/11 (27% of audited sites)	96/347 (27.2%)	2/11 (18%)	3/13 (23%)	Yes – except Lenart, Porvaneckas and Slappendal
RECORD 2 (123 sites)	13/2509 (0.5%)	131/24/0	NA	2/7* (29% of audited sites)	55/216 (25.5%)	2/7 (29%)	4/10 (40%)	Yes – except Corces, Yang Naraffete, and Ono
RECORD 3 (147 sites)	9/2531 (0.4%)	37/2+/0	NA	1/3 (33% of audited sites)	28/70 (40.0%)	1/3 (33%)	1/5 (20%)	Yes – except Brabants
RECORD 4 (130 sites)	1227/3148 (39.0%)	265/61/8	504/28	3/9* (33% of audited sites)	197/312 (63.1%)	6/9 (67%)	8/16 (50%)	No

*1 additional site each from RECORD 2 and 2 additional sites from RECORD 4 had critical drug accountability issues identified during FDA inspections.

DSI Assessment of RECORD 1 Reliability: DSI recommends that the data from this study can be used in support of the NDA. Although there were drug accountability issues identified at 27% of (b) (4) audited sites in RECORD 1, monitoring was assessed as adequate in the majority of subjects and sites, and earlier FDA inspections did not reveal drug accountability issues. Based on review of (b) (4) audit findings, however, there were 3 sites in RECORD 1 (Lenart, Porvaneckas, and Slappendal) for which DSI cannot assure data reliability (due to drug accountability issues). DSI acknowledges that there were unreported adverse events from this trial, and suggests that the review division consider additional events identified during the audit process in their safety analysis. There were no unreported SAEs noted from RECORD 1. Postoperative randomization did not occur to any significant degree in RECORD 1. In summary, despite some identified deficits in study conduct, the deficiencies do not appear pervasive enough to cast doubt on the overall reliability of RECORD 1 study data.

DSI Assessment of RECORD 2 Reliability: DSI recommends that the data from this study can be used in support of the NDA. Although there were drug accountability issues identified at 29% of (b) (4) audited sites in RECORD 2, monitoring was assessed as adequate in the majority of subjects and sites and the number of audited sites is relatively small, and earlier FDA inspections did not reveal drug accountability issues. There were 4 clinical investigator sites in RECORD 2 (Corces, Yang, Naraffete, and Ono) for which DSI cannot assure data reliability (due to drug accountability issues and/or issues with source documentation). DSI acknowledges that there were unreported adverse events from this trial, and DSI suggests that the review division consider additional events identified during the audit process in their safety analysis. There were no unreported SAEs noted from RECORD 2. Postoperative randomization did not occur to any significant degree in RECORD 2. In summary, despite some identified deficits in study conduct, the deficiencies do not appear pervasive enough to cast doubt on the overall reliability of RECORD 2 data.

DSI Assessment of RECORD 3 Reliability: DSI recommends that the data from this study can be used in support of the NDA. Although there were drug accountability issues identified at 33% of (b) (4) audited sites in RECORD 3, a very small number of RECORD 3 sites were audited by (b) (4) making the statistical assessment of this finding problematic. Monitoring was assessed as adequate in 42 of 70 (60%) of subjects and 2 of 3 sites audited by (b) (4) Based on Falcon's monitoring audit strategy of focusing on a PDC (Patient Data Check) form for evaluation of monitoring adequacy, it appears that up to 40% of subjects had inadequacies in monitoring. However, note that DSI's assessment of adequacy of monitoring and data reliability did not solely focus on the PDC form, but rather on the specific types of issues that were missed by monitoring and their impact on assessment of key safety and efficacy parameters. There was 1 site in RECORD 3 (Brabants) for which DSI cannot assure data reliability (due to drug accountability/storage condition issues identified during (b) (4) audit). DSI acknowledges that there were unreported adverse events from this trial, and DSI suggests that the review division consider additional events identified during the audit process in their safety analysis. There were no unreported SAEs noted from RECORD 3. Postoperative randomization did not occur to any significant degree in RECORD 3. In summary, despite some identified deficits in study conduct, the deficiencies do not appear pervasive enough to cast doubt on the overall reliability of RECORD 3 data.

DSI Assessment of RECORD 4 Reliability: FDA inspections, the (b) (4) audits, and the (b) (4) data verification process have identified serious issues with the study conduct and monitoring of the RECORD 4 study. Postoperative randomization in violation of the protocol occurred at 1227 of 3148 (39%) of RECORD 4 subjects, despite a memo from the CRO monitoring the study ((b) (4) that postoperative randomization was not acceptable. Although this occurred equally in both study arms, the possibility exists that because of postoperative randomization, the labeled population would not be reflective of the actual study population. The number of unreported adverse events detected by (b) (4) monitors (265) was more than twice the number from any of the other RECORD trials (110, 131, and 37 for RECORD 1, 2, and 3, respectively), and there were 504 unreported adverse events detected during the (b) (4) data verification; the review division may wish to review these adverse events for safety analysis inclusion. All newly reported serious adverse events were from RECORD 4 sites: 8 from the (b) (4) audits and 28 from the (b) (4) data verification. In addition, there were serious drug accountability issues at 3 of 9 (33%) of (b) (4) audited RECORD 4 sites, in addition to 2 sites with serious drug accountability issues identified earlier by DSI (Corces and Esquivel). The (b) (4) audit finding that 197 of 312 (63%) of subjects and 6 of 9 (67%) of sites in RECORD 4 were monitored inadequately by (b) (4) is striking, and higher than the other RECORD studies.

Eight of 16 (50%) sites of the RECORD 4 sites audited by (b) (4) or inspected by FDA ended with an evaluation that the data from the sites was not reliable, reflective of drug accountability deficiencies and other violations of good clinical practice, including postoperative randomization, falsification, missing records, and improper study drug storage. DSI does not feel that the data verification process conducted by (b) (4) has been validated, nor does it negate the findings described above. It is important to note that these sites audited by (b) (4) represent only 7% of total sites and 10% of total subjects in the RECORD 4 study. The additional audits were conducted with the expectation that failure to identify additional sites with serious deficiencies would provide assurance that the remaining unaudited sites provided reliable data. The pervasive nature of study conduct deficiencies, including particular inadequate monitoring, raises the possibility that there may be deficiencies affecting the primary efficacy outcome which were not detected, e.g. venography conduct. Based on serious drug accountability issues, a relatively large number of unreported adverse events and serious adverse events, a high rate of postoperative randomization in violation of the protocol, and inadequate monitoring of a majority of the RECORD 4 sites as well as the relatively small proportion of sites audited, DSI recommends that the data from RECORD 4 be considered to be unreliable. While the Applicant attempted to provide further assurance that data from this study was reliable via the (b) (4) data verification process, (b) (4) findings do not negate the findings described above. Recall that the (b) (4) audit proposed by J&J was intended to be a specific methodology for analysis of the audited data, not the performance of 3rd party audits, per se, and that FDA did not agree or review as to the usage of this methodology for this intended purpose.

VI. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Executive Summary Conclusion

DSI finds that Johnson and Johnson's response to the FDA's May 27, 2009 Complete

Response Letter addresses all of the DSI items requested in the CR Letter. However DSI's review concludes that the data generated by the RECORD 4 study is unreliable, and recommends that the data not be used in support of the respective indication of prophylaxis of deep venous thrombosis and pulmonary embolism after total knee arthroplasty. Given serious drug accountability issues, a relatively large number of unreported adverse events and serious adverse events, a high rate of postoperative randomization in violation of the protocol, and inadequate monitoring of a majority of the RECORD 4 sites as well as the fact that only a subset of sites have been audited, DSI cannot provide a favorable assessment of RECORD 4 data reliability for the remaining 88% of uninspected/unaudited clinical investigator sites based on extrapolation of the (b) (4) audit findings. Although issues exist with the study conduct of RECORD 1, 2, and 3, they are not sufficiently pervasive to reflect negatively on overall study data integrity, and the data from these 3 studies are considered to be reliable, with the exception of a few sites.

Summary Assessment and Recommendation

On May 27, 2009 FDA issued an NDA Complete Response letter to Johnson & Johnson for the Xarelto NDA 22-406 for the indication of prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery. Prior to submission of this NDA, FDA inspections based on complaints received resulted in one Warning Letter and one NIDPOE, as well as an investigator being discontinued by the sponsor due to failure to maintain clinical trial records. Inspections conducted in support of the NDA resulted in four OAI classifications, five VAI, and two NAI. Evaluation of the inspections revealed serious deficiencies in adverse event reporting, drug accountability and administration, and adherence to the protocol especially postoperative randomization. Also of serious concern were deficiencies in monitoring noted at the inspected CI and sponsor sites noted in all four RECORD studies, but particularly pervasive in RECORD 4. The CR Letter requested, in part, evidence that the four RECORD studies are reliable, and proposed that independent third party audits be conducted at additional CI sites to provide reassurance of the reliability of the RECORD 1, 2, 3, and 4 study data.

Johnson & Johnson submitted a CR on December 23, 2010. (b) (4) was selected to conduct the third party independent audits. There were 30 clinical sites audited across all four RECORD studies: all 18 high enrolling sites (previously uninspected) with > 60 randomized subjects and 12 moderately enrolling site with 15-59 randomized subjects randomly selected. All subjects at sites were audited if there were less than 35 subjects; otherwise, a random sample sufficient to provide 95% confidence to rule out a 5% error rate was chosen. Audits of these 30 sites resulted in audit of 950 subjects out of 12,729 total, which constituted 7.5% of all subjects in the 4 RECORD studies. The parameters examined during the audits were adequacy of monitoring, adverse event reporting, adherence to protocol including postoperative randomization, informed consent, investigational product, and source data verification and CRF completion. Also submitted with the CR were the reports of the Bayer audits.

Adequacy of clinical trial monitoring was assessed in several ways. (b) (4) auditors stated that overall site study monitoring was deficient at 1 of 11 (9%) of RECORD 1 sites, 2 of 7 (27%) RECORD 2 sites, 1 of 3 (33%) RECORD 3 sites, and 5 of 9 (56%) RECORD 4 sites; key efficacy and safety findings were missed during monitoring of these sites. Assessment of

monitoring by individual subjects resulted in the following assessment of inadequate monitoring: RECORD 1 96/347 (27.2%) subjects; RECORD 2 55/216 (25.5%) subjects, RECORD 3 28/70 (40.0%) subjects, and RECORD 4 197/312 (63.1%) subjects. Lastly, Johnson & Johnson submitted the results of 74 clinical investigator site audits conducted by Bayer; 69 were routine. Significant findings noted during the (b) (4) audits at the sites of Drs. Lenart (RECORD 1), Porvaneckas (RECORD 1), Nararrete (RECORD 2), and Buettner (RECORD 4) were not mentioned in the Bayer audit reports. FDA inspectional findings at the sites of Dr. Michael Murray (RECORD 4) were not described in the Bayer audit, nor did the Bayer audits detect the most serious deficiency which resulted in disqualification of Dr. Craig Loucks (RECORD 4). Inspection of Bayer as the sponsor of the NDA revealed some monitoring deficiencies as well, in that the major issues at the sites of Drs. Corces (RECORD 2) and Murray (RECORD 4) were not identified by Bayer monitoring. Monitoring for the RECORD 1, 2, and 3 studies was performed by Bayer, while the monitoring for RECORD 4 was conducted by the CRO (b) (4) Although issues with clinical trial monitoring inadequacies were present in all four RECORD trials, the deficiencies were most frequent in the RECORD 4 study. Deficiencies in clinical trial monitoring raise serious concern regarding the validity of data submitted in RECORD 4. In particular, the widespread monitoring deficiencies do not provide reassurance that study conduct deficiencies are not present at the approximately 90% of RECORD 4 sites which were not inspected by FDA or audited.

Based on DSI's assessment of (b) (4) audit reports, drug accountability deficiencies were present at 3/11 (27%) of RECORD 1 sites, 2/7 (29%) of RECORD 2 sites, 1/3 (33%) of RECORD 3 sites, and 3/9 (33%) of RECORD 4 sites. Site drug accountability was considered deficient if source documentation for key efficacy assessments was absent and/or there were significant issues with documentation of drug accountability such that it does not appear possible to verify that subjects at the site received study drug. Further information from Johnson & Johnson was requested that might provide assurance of drug administration at the problematic sites, such as pharmacy or nursing records. For the sites assessed as deficient here, no such documentation was located. Note that a very small number of RECORD 3 sites were audited by (b) (4) making the statistical assessment for this study problematic. We acknowledge the finding that 27-33% of RECORD 1-3 sites had deficiencies in drug accountability; however these findings were not replicated in FDA inspectional findings. In contrast with RECORD 4, however, audits of the RECORD 1, 2, and 3 studies did not demonstrate systematic deficiencies in multiple aspects of clinical trial conduct, such that data integrity from all study sites must be questioned. However, the findings that 33% of RECORD 4 sites audited by (b) (4) (as well as 2 additional sites, Corces and Esquivel, identified earlier by DSI) had serious drug accountability deficiencies, 67% had inadequate monitoring, and 50% of sites audited or inspected were determined to provide unreliable data, together indicate that the data from RECORD 4 cannot be considered reliable.

Failure to report adverse events was identified at all but 2 sites audited by (b) (4) There were 110 unreported AEs in RECORD 1, 131 unreported AEs in RECORD 2, 37 unreported AEs in RECORD 3, and 265 unreported AEs in RECORD 4. There were 8 unreported SAEs noted in the (b) (4) audits, all in RECORD 4. When the unreported AEs were individually examined for significance as defined by the necessity for expeditious medical evaluation, or were AEs involving bleeding or hepatic events, there were 16 in RECORD 1, 24 in RECORD 2, and 265

in RECORD 4; RECORD 3 could not be tabulated due to failure to list individual laboratory abnormalities. During the (b) (4) data verification process of RECORD 4, 504 unreported AEs were noted, as were 28 previously unreported SAEs. The (b) (4) audits identified more than twice as many AEs in RECORD 4 than in the other RECORD studies, and all of the unreported AEs were from RECORD 4. The high number of unreported AEs and SAEs from RECORD 4 may impact labeling for safety, and is again reflective of inadequate monitoring of RECORD 4.

Failure to adhere to the protocol, in particular postoperative randomization, occurred in 39% of RECORD 4 subjects. Although postoperative randomization would not be expected to affect the primary efficacy outcome since it occurred in both study arms, the concern remains that the population described in the product label may not be reflective of the actual study population if subjects are screened and enrolled by criteria other than those in the protocol. There was no other evidence of widespread failure to adhere to the inclusion criteria, and there was no significant postoperative randomization in RECORD 1, 2, or 3. Again, the failure of the CRO (b) (4) to enforce compliance with the protocol requirement for preoperative randomization is reflective of inadequate monitoring of RECORD 4.

The (b) (4) audits of the RECORD 4 study sites were conducted in an attempt to provide assurance of the validity of the data from RECORD 4. There was no difference in primary efficacy or safety outcome when sensitivity analyses were conducted on high versus low quality sites or investigators or on subjects randomized preoperatively versus postoperatively. Although interesting, the (b) (4) methodology is not validated, nor does it address the effects of inadequate monitoring of RECORD 4, which may have introduced unidentified errors not accounted for in the data verification.

In summary given the pervasive findings of deficient clinical trial monitoring, high number of clinical investigator sites with data assessed as unreliable, failure to follow the protocol including postoperative randomization, and deficient clinical trial conduct including failure to report significant adverse events and SAEs, DSI cannot provide a favorable assessment of RECORD 4 data reliability for the remaining unaudited sites based on extrapolation of the (b) (4) audit findings. Although some issues exist with the study conduct of RECORD 1, 2, and 3, they are not sufficiently pervasive to recommend an unfavorable assessment of data reliability. Therefore, the data from RECORD 1, 2, and 3, with exception of select sites as identified earlier, are considered reliable in support of the application. The data from RECORD 4 are not considered reliable in support of the respective indication.

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APPENDIX 1 SUMMARY OF [redacted] (b) (4) AUDIT REPORTS

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	[redacted] (b) (4) Rating C=Critical M=Major m=minor	Bayer or [redacted] (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
RECORD 1						
Bauer Austria 44003	Y	N	M	N	S	Subject 154759 was not appropriately treated for HTN, had a CVA 1 day after surgery. 4 unreported AEs: iron deficiency, diuresis, diarrhea, elevated GGT = 205
			m	N	B	12 study conduct deficiencies noted in 35 audited, including no source documentation of local lab assessments for all 35
			m	N	B	16 subjects of 35 audited subjects had discrepant entries SD vs. CRF (e.g., wound drain volumes, VS)
Kruczynski Poland 18009	Y	N	C	N	S	7 subjects randomized prior to documented eligibility evaluation; all eventually met eligibility criteria
			M	N	S	For all subjects who experienced AEs, the severity and relationship to study drug was not documented.
Lenart Hungary 46002	N	N	M	Y	S	No documentation in study files that the local IEC was notified of the 5 SAEs at this site
			M	?	E	**Study Coordinators log used to document drug accountability and dosing for all subjects, but entries in log are not signed and dated/initialed; medications and infusions administered to the study subjects recorded inconsistently; no documentation of subject training on injection techniques, dosing instructions, proper storage of study drug**.
			M	N	B	2 subjects received two pre-surgical study drug injections, as surgery was rescheduled.
			M	N	S	Preoperative laboratory results/ECGs not consistently signed and dated by investigator.
			M	N	S	For AE reporting, no source is given for seriousness, action taken with study drug, treatment, severity, and relatedness.
			m	N	B	8 subjects of 35 audited had discrepant entries SD vs. CRF, e.g. medical history, Xanax dosage

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Marinoni Italy	Y	N	M	?	S	1 subject had a hx of disturbed vision and ITP, had a "pre-retinic" hemorrhage on Day 1, study drug continued
22001			M	N	B	Source documentation deficient for all subjects enrolled: No statement Day 1 to confirm eligibility, PE/clinical assessments not recorded in source notes, entries in source notes not signed/dated, ECGs signed , not dated.
			M	N		Out of range labs not routinely annotated as "clinically significant", 1 subject with CPK elevated before and after randomization (1172) not signed or assessed by PI.
			M	N	E	Source therapy logs were not always clear as to which medication had been prescribed/dispensed and changes were made to the data in the logs for several subjects which were not initialed/dated. 3 examples cited, including 2 doses of study drug.
			M	N	S	4 subjects had their epidural catheter inserted/removed outside protocol mandated timelines; none of these catheters were recorded on the CRF. Two were placed too soon after study drug administration (1.5 and 2 hrs) and 2 were withdrawn too soon after study drug admisntraiton (1.5 and 4 hrs after dose), rather than 2X the half-life.
			M	N	S	4 subjects had unreported AEs: left lower limb paresthesia, leg edema, abnormal ECG, wound erythema/edema
			M	N	S	SAE of "infection of the surgical site" noted 10/3/06, reported late on 10/31/06
			m	N	B	6 of 15 subjects the site had discrepant entries SD vs. CRF, e.g., medical history, fever. Some source documentation was missing at the site: 1 subject central lab reports and lab culture report, 2 subjects hematology reports, and 2 subjects medical history.
			In text, not cited	N	E	3 subjects had local lab test reports during active treatment period with coagulation parameters, potentially unblinding the study team.
Mazurkiewicz Poland	Y	N	M	N	B	Documentation of PI involvement with study subjects lacking.
18019			M	N	S	4 subjects with unreported AEs: anxiety and noncooperation, cholelithiasis, and constipation in 2 subjects
Peidro	Y	N	C	N	B	1 medical record missing during audit

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Spain 24002			M	Y	B	Source documents for 12 of 19 subjects audited were missing/incomplete/not recorded to GCP standards (failure to sign/date labs, missing lab reports and/or ECGs, absent venogram results). AE descriptions in progress notes did not include severity, relationship to study drug, and outcome; this info was in eCRFs. No statement in progress notes or Inclusion/Exclusion checklist in records to document eligibility (11 of 19 subjects audited).
			M	N	B	Protocol and sponsor study procedure violations in 12 subjects (e.g., baseline ECGs not signed, date of last study medication not found in source notes, no pregnancy test, no source documentation for vital signs at Day 13, Day 36, and/or Day 65).
			M	Y	S	6 of 19 subjects audited had unreported AEs: hand edema, low potassium, nausea x 3, disorientation/anxious/depression, skin candidiasis. No SAE assessment documented for wound infection
			m	N	B	In 8 of 19 subjects audited, discrepant entries SD vs. CRF, including concomitant medications and medical history
			m	N	B	No training documentation on file for subinvestigators, and the study nurses were not identified on the Site Personnel Responsibility Log.
Pesola Finland 59005	Y	N	M	N	S	2 subjects had unreported AEs: sore calf, nausea/vomiting
			m	N	S	15 of 35 subjects audited had a single laboratory or ECG study outside of the protocol specified window.
Porvaneckas Lithuania 57001	N	N	M	N	S	The site's copy of the IC document contains only the last two signature copies.
			M	N	E	**Study drug administration times were exactly the same for each of the 34 subjects audited; exact dosing times were not documented, and it is unknown how close to the predicted time doses were given.** Pregnancy test or contraception information was missing for 2 subjects.
			M	N	S	There were unreported AEs in 12 of 34 audited subjects. Examples: suspected allergic skin reaction, hypotension, elevated blood pressure, fungal infection.

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			M	N	S	No verification sponsor notification of SAE within 24 hours were available at the site for 6 of 7 SAEs
			m	N	B	9 of 34 audited subjects had eCRF information that could not be verified in the source data or discrepancies between the source data and the eCRFs, including absence of time of blood transfusion in eCRF and in 2 subjects, discrepancy in time of study drug administration (4 and 1 hour differences).
			m	N	B	Whiteout was used to correct source documentation errors in 2 subject records
Schwartsmann Brazil 50006	N	N	M	N	B	Physical exams were not performed on Day 1, 6, 13, 36, and 65 for all 35 subjects audited in violation of the protocol.
			M	N	B	For all 35 subjects audited, post-discharge clinical assessments are not documented on the source document. For all 35 subjects audited, information entered on the source document is not signed/initialed or dated.
			M	N	E	[a]*For all 35 subjects audited, documentation of study drug administration during the inpatient phase is captured only on progress notes as "administered dose of study 11354 medication per protocol at XXX [time]". It is not clear whether the tablet or syringe were administered, or both, were administered.* *8 of 35 subjects audited lacked documentation of a single dose of study drug; 1 additional subject lacked documentation for Days 1-6.* *Documentation of study drug administration in the medical record was not contemporaneous for 4 of the 35 subjects audited.*
			m	N	B	For 5 of 35 subjects audited, discrepancies were noted between eCRF and source documents. Examples include absent eCRF entries for concomitant medication, medical history omitted from eCRF, study medication administration time discrepancy of 6 minutes
Slappendel Netherlands 30002	N	Y	M	N	B	Documentation of PI oversight, delegation, and training of study staff was deficient. Investigator review of study document was inadequate.
			M	N	B	For all 35 subjects audited, there is no documentation of protocol-required

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						physical examinations and clinical assessments for any visit days. 1 subject was randomized 2 days prior to informed consent being obtained.
			M	Y	E	[b]**10 of 35 subjects audited had drug accountability records which were incomplete and/or discrepant with other subject source documentation.**
			M	N	S	21 subjects had 54 unreported AEs. Examples include shortness of breath, hematoma around wound, tachycardia, fever, bradycardia. AE reporting for all audited subjects did not include a source of seriousness, action taken with the study drug, treatment, severity, and relatedness for AEs and/or bleeding events.
			M	Y	E	Source documentation was deficient for all audited subjects. Examples include SDWs not signed or dated for any visit days and absence of a medication record for the subject's hospital stay. **No source documentation to support the date and time of the pre-operative self administered injection of enoxaparin/placebo by the subjects or the date and time of last outpatient dosing for all subjects.**
Stehlik Czech Republic 38007	Y	N	M	N	S	1 subject had study related procedures performed prior to signing the informed consent document.
			M	N	S	There were 12 unreported AEs in 11 subjects of 34 subjects audited. Examples: Anxiety, hematoma, hypotension with chest pain, UTI, left leg swelling. No documentation in source to support the eCRF entries for severity of the AE or relationship to the study medication; the information was recorded directly onto the eCRF
			M	N	B	For 13 of the 34 subjects audited, the surgery start and stop times recorded in the eCRF could not be verified from the source documentation. Given this inconsistency, it could not be determined if the investigator complied with the minimum 6 hour post surgery study medication administration requirement.
			m	N	B	For 9 of 34 subjects audited, there were discrepancies noted between eCRF and source documents. Examples include failure to record Zyrtec as a

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						concomitant medication on the CRF, incorrect date for a pregnancy test, medical history omitted from eCRF, discrepancies in BP.
RECORD 2						
Belickas Lithuania	Y	N	M	N	S	2 SAEs were reported to the sponsor more than 24 hours after site awareness; each SAE was reported after approximately 3 months.
57001			M	N	S	7 of 35 subjects audited had unreported AEs: low hemoglobin x 3, fever x 2, RUQ pain, nausea, elevated potassium (6.2).
			M	Y (some)	B	Deficiencies, omissions, and deviations from GCP were noted in the source documentation. Examples include: alteration of dates and numbers on 2 or 3 of the local lab report slips with no explanation, missing randomization confirmation for 2 subjects, at least 95% of all blood pressure measurements appeared to be estimated or rounded, use of correction fluid was noted on progress notes.
			m	N	E	Discrepancies in number of tablets/injections returned vs the number that should have been returned for 6 subjects of 35 audited. However, compliance was not outside the protocol-allowed 80-120%.
			m	N	S	The site maintained only the last two pages of the informed consent document containing signatures for all subjects.
			m	N	B	Source documentation was inconsistent with eCRF entries for 14 of 35 subjects audited. Examples include concomitant medications not recorded on the eCRF, drainage volume inconsistency, estimated surgical loss.
			m	N	B	Dr. Belickas was not included on the Site Personnel Responsibility Logs. The assigned tasks on these logs did not include clinical assessments for safety or efficacy for the sub-investigators who performed the majority of these assessments.
Dhanjee South Africa 37001	Y	N	M	N	S	There were 4 unreported AEs: fever, calf pain, backache, and hypotension.
Field England 12008	Y	N	M	N	B	There was minimal documentation of PI involvement in the study
			M	N	S	It was unclear whether SAE reporting timelines were adhered to for 7 SAEs; reporting occurred after 3 weeks – 1 year to the sponsorfor these SAEs.

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			M	N	S	There were 21 unreported AES in 13 of the 43 subjects audited. Examples include: low hemoglobin, swelling left leg
			m	N	E	2 subjects of 43 audited had discrepant drug administration/accountability information (4 vs. 6 tablets returned, 80 minute discrepancy in drug administration time.)
			m	N	B	Discrepancies were noted between eCRF entries, SDW, and medical record information for 6 of 43 subjects audited. Examples include laboratory draw and ECG times, concomitant medication, one instance of study drug administration.
			m	N	S	Medical history in the medical record not captured in eCRF in 17 of 43 subjects audited. Examples include penicillin allergies, glaucoma.
			m	N	S	For 2 subjects laboratory pages were not signed or clinical significance documented by the PI 1 subject had a history of CRI per medical records, no screening labs documented to be reviewed prior to surgery (b) (4) screening labs signed by PI 10/14/06, subject withdrawn due to elevated BUN/Cr on 10/13/06.
			m	N	S	Qualifying information for AE data captured on eCRF (relationship to study drug, action taken, seriousness, and severity, not recorded in source documentation
			m	N	E	1 subject had venography performed unilaterally with no documentation as to reason.
Martson Estonia 63002	Y	N	M	N	B	2 subjects were enrolled despite allergy to contrast and thyroid condition; venography could not be performed for these 2 subjects.
			m	N	B	5 of 35 subjects audited had protocol deviations, including study visits out of window, venography performed too close to last dose of study drug.
			m	N (missed #3/3)	B	3 of 35 subjects had eCRF entries not supported by source documentation (no screening ECG interpretation, no reason for drug discontinuation (rash), AE of pain after venography dated earlier than venography).
			M	N	S	8 of 25 subjects had unreported AEs. Examples: thigh hematoma, swelling right foot, anxiety, knee pain
Nafarrete	N	N	M	N	B	3 of 25 medical charts could not be located

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Mexico 32005			M	?	B	**Study drug administration times were exactly the same for each subject for all subjects audited; exact times could not be documented.** 3 subjects had study drug administered too early after wound closure (1-5 hours)
			M	N	S	There were 35 unreported AEs in 10 of 25 subjects. Examples: anemia, infection, vomiting
			m	N	B	Lapses in GCP documentation were noted, including ECG tapes stapled into patient charts without identifying information, white-out in several patient charts, and an SAE report completed in pencil.
			m	N	B	Concomitant medications were listed in the medical chart, but were not reported in the CRF in 5 of 25 subjects audited: examples include magnesium sulfate, neupogen; fraxinhearina; metoclopramide, morphine, Graten, neumerabraum; metoclopramide, decorex; bicarsol, fentalyn, Dobutrex, dermakin, dopamine, precedex dexmedetomidine hydrochloride.
			m	N	B	5 of 25 subjects had discrepancies between the source data and the CRFs, including height/weight, date of ECG, side of surgery, wound drainage volume, date of ECG
			m	N	B	11 of 25 subjects had information on the CRFs that could not be verified in the source documentation. Examples include misplaced ECGs, no vital signs in source documents, no height/weight in source document, venography procedure/results absent from source document.
Ono Brazil 50005	N	Y	C	Y	E	**Documentation of study drug administration during inpatient phase of study was missing or deficient: 8 subject records contained very few notations that study drug had been given, and the remaining 16 records contained none.** **Doses of study medication documented only on SDW were not signed/initialed or dated, so it is unclear whether they are primary source entries.**
			C	Y	B	**Discrepancies were noted among eCRF entries, SDW entries, and medical chart information – 73 discrepancies for 20 subjects. Examples include surgery start/stop times, intraoperative blood loss, drain**

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						volumes.
			M	Y	B	PI oversight of study conduct was deficient – PI unaware of study procedures, no evidence that he participated in study conduct, not present in monitoring visits, and he was unaware of how many SAEs were reported from his site.
			M	Y	B	For 11 of 24 enrolled subjects, Day 1 physical examinations and clinical assessments were either not recorded or could not be verified due to missing charts.
			M	Y	S	Documentation of medical oversight was inadequate. Potential AEs were not reviewed or evaluated by a study physician; 1 subject who received 2 pre-surgery doses of enoxparin/placebo injections due to surgery rescheduling, had suctioning of blood from the nasal cavity, 2 subjects had elevated BP on 5 occasions without Rx or recorded as AEs.
			M	Y	S	5 subjects had informed consent granted by a "witness" rather than by the subject. The consent process was not documented in the medical charts for any of the subjects enrolled.
			M	Y	B	Source documentation was found to be deficient for all subjects: post-discharge PEs/CAs were not captured on the SDW; much of the information captured on the SDW had not signatures/initials/dates; information appeared to be transcribed for the medical record to the SDW, but many discrepancies were noted; central lab results were not reviewed in a timely fashion; screening ECGs were not reviewed by an MD until after randomization.
			M	Y	S	37 unreported AEs in 16 subjects. Examples include hypertension, nasal bleeding during surgery, edema, mental confusion.
			C	Y	B	1 medical record could not be located
Wang China 54001	N	Y	M	Y	S	4 of 6 women of child bearing potential did not have pregnancy tests performed prior to enrollment in the trial.
			M	Y	B	30 of 35 subject audited had discrepancies between eCRF and medical chart information. Examples include surgery start/stop times, concomitant medications, blood transfusion and venography absent from source records,

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			M	N	B	Deficiencies were noted pertaining to source documentation including: failure to document hx of alcohol abuse; PCA not listed as concomitant medications; copies of venography films sent to the adjudication committee were not kept for 13 of the 84 subjects at the site.
			M	N	S	There wers 18 unreported AEs in 14 subjects of 35 audited, including hypertension and dyspnea.
			M	N	B	4 subjects had study conduct issues identified: Discontinuation of enoxaparin/placebo 1 day late; receipt of contraindicated medication Fragmin; failure to provide clinical evaluation of lipase = 86; placement of spinal needle/epidural catheter 2 hours early in 2 subjects
			M	N	E	Source documentation of study drug administration and blood sampling times were listed as occurring at the same time for 12 of 35 subjects audited
			m	N	E	Investigational product documentation was found to be deficient in 8 of 35 subjects audited regarding doses expected vs actually returned. Compliance was not outside the 80 – 120% allowed per protocol.
			m	N	S	24 of 35 subjects audited did not have documentation of the informed consent process in the source records
RECORD 3						
Brabants Belgium 28015	Y	Y	C	Y	E	**Exact time of study drug administration was rarely recorded on the inpatient medication administration records for any of the 27 subjects – only on grid with 0800, 1200, 1600, and 2000 grids.** **Times of study drug administration frequently do not match the times noted on the inpatient medication administration sheet.**
			C	Y	B	**Study coordinator was unable to define a consistent primary source for many of the data points, including drug dosing, surgery start/stop times, and laboratory draw times.** PCAs were not verifiable in medical records Significant portions of source records were missing for 4 subjects. The start times of multiple activities were noted as occurring simultaneiously or at overlapping times in the source. Examples: oral & injectable IP; venography & lab draws.

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			M	Y	B	Documentation of PI oversight and delegation of study conduct was deficient
			M	Y	S	Documentation of medical oversight by the study was inadequate: source documentation of AEs and DVTs was missing qualifying data (stop date/time, severity, relationship, and outcome) and there were 36 unreported AEs in 20 subjects of 27 audited. Example = leg hematoma.
			M	Y	E	Documentation of investigational product accountability and storage conditions during the inpatient phase of the study was inadequate. **Drug accountability logs provided by Bayer were not used by the study coordinator to record drug accountability. Temperature in study drug storage area was monitored weekly, not daily.**
			M	?	S	In 9 of 27 subjects, screening procedures were conducted prior to written consent or outside of study-proscribed windows, including screening ECGs and laboratory studies
			M	Y	S	6 subjects had significant protocol deviations, including receiving study drug tablet and injection and Fraxiparine, study drug injection fewer than 12 hours and 10 hours after surgery in 2 subjects, first dose given 1.5 hours after surgery (not 6-8 hours after)
Paulsson Sweden 34003	N	N	M	N	S	1 unreported AE in 19 subjects: constipation
			m	N	S	5 subjects had source document deficiencies regarding 7 AEs: 1 subject relationship and severity in eCRF not source; 6 AEs were in eCRF not source
Synder Poland 518008	Y	N	C	N	E	All subjects received 1 or more doses of study medication outside the protocol-specified window (10 subejcts-1 dose, 9 subjects-2 doses). Time outside dosing interval ranged from approximately 2 to 5 hours
			M	N	E	6 subjects of 19 had discrepancies between eCRF and source documentation, including laboratory draw date, whether a dose of study medication was given, injection time.
			M	N	S	5 subjects of 19 had missing or incorrect PI signature and/or dates on lab reports

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			M	N	B	1 subject had an illegible time of transfusion on the source documented corrected by the monitor
			m	N	B	Correction fluid and pencils were used on the records of 1 and 2 subjects respectively and all subjects had sticky notes used as source documentation for vital signs.
RECORD 4						
Dessouki Canada 26016	Y	N	C	?	S	1 subject was hospitalized for acute cholecystitis and subsequent cholecystectomy; no SAE was reported to the sponsor or REB.
			M	N	S	1 subject had ALT = 182 on Day 13 (4x ULN). Retesting not done until 1 month later, no monitoring as specified in the protocol. PI documented this value as "NCS"
			M	Y	B	Deficiencies in documentation were noted including: approximately 75% of subjects had an alteration in the time stamp on original ECGs; 3 subjects had no documentation in source that subjects had stopped Metformin 2 days prior to venography and restarted at the earliest, 2 days after venography; most vital signs were not taken in the supine position after 5 minutes rest, as specified in the protocol; approximately 75% of the subjects audited had an AE of "post-op nausea" recorded due to receiving Gravol prophylactically, despite no source record indication of nausea; a local lab CBC including INR was obtained at Day 13 for one subject, which may result in unblinding.
			M	N	B	7 subject records were apparently backdated by the PI (lab reports, ECG, SDW worksheet).
			M	N	B	There were discrepancies between eCRF and source documentation for 7 subjects. Examples include for qualifying information for 2 AEs, ECG recorded as normal on eCRF but ECG itself read as atrial premature complex, right axis deviation, RBBB, and old inferior MI
			M	N	S	There were 18 unreported AEs in 15 of the 35 audited subjects. Examples include shaking with fever &hallucinations, drug-induced pancreatitis, elevated GGT = 275, ARI, decreased platelets, NA = 119 with K = 2.5, irregular HR, Tx 2 U PRBCs, burning calf
			M	N	S	There was no documentation that the 3 SAEs initially identified by the site

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						and reported to the sponsor were reported to the REB.
			m	N	B	No evidence that sub-investigators or study coordinators had been trained on their study-related duties
			m	N	E	18 of 35 subjects audited were randomized on the day of surgery. It was not possible from the data at the site to determine whether randomization occurred postoperatively
Hollman U.S.A, Florida 14023	Y	N	M	Y	S	6 of 35 subjects audited had unreported AEs including leg muscle spasm, rash on buttocks
			m	Y	E	Protocol violations were noted in 4 of 35 subjects audited including 1 subject randomized postoperatively
			m	Y (CAD)	S	Discrepancies were noted between source documentation and eCRFs for 8 subjects. 1 subject who refused a venogram on Day 13 and "withdrew consent for the study" per 2 site emails; however, the subject was not withdrawn from the study and continued study-related blood draws through day 42. 1 subject had coronary artery disease noted in the medical history but not recorded on the eCRF.
			m	Y	E	34 of 35 subjects were randomized on the day of surgery. Data at the site did not allow determination of which subjects were randomized postoperatively.
Jove U.S.A, Georgia 14016	Y	N	C	Y	S	1 subject was enrolled despite evidence of current EtOH abuse and elevated GGT at screening (1499)
			M	Y	E	Discrepancies were noted between eCRF and medical charts for 26/39 subjects audited. Examples include 1 dose of enoxaparin/placebo recorded in medical record not eCRF, discrepant drain volumes, discrepant vital signs, onset dates of AEs.
			M	N	S	For 2 of 4 SAEs that occurred in this audit sample, it could not be determined whether or not the SAE was reported to the sponsor within 24 hours.
			M	N	B	Data were not captured according to site practices: eCRF start and/or stop times of surgery are inconsistent with the site's practice of using operative start/stop times (2 subjects); intraoperative blood loss in eCRF is

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						inconsistent with the site's practice of using the intraoperative report to obtain blood loss (10 subjects); blood transfusion start times in eCRF are inconsistent with the site's practice of using the time pasted into the medical chart (3 subjects)
			M	Y	S	33 AEs in 13 of 39 subjects audited had unreported AEs. Examples include fever, hypotension, UTI.
			M	N	S	Drainage volumes in electronic nursing assessment system were difficult to reconcile with drain volumes in the eCRF.
			m	N	B	Training was not documented for any of the subinvestigators listed on the Form 1572 and Delegation Log.
Kilgore U.S.A., Florida 14034	Y	N	C	Y	S	25 of 35 subjects audited had 29 unreported AEs. Examples include SOB, elevated AST/ALT/GGT/alkaline phosphatase
			C	Y	B	9 of the 35 subjects audited had protocol deviations detected. Examples include 6 study visits occurring 3 days out of window, screening ECG done prior to signing of informed consent, failure of PI to sign abnormal lab report (BUN, ALT, & LD).
			M	N	S	4 of the 35 subjects audited had deficiencies in source documents, including failure of the PI to assess abnormal lab values and ECGs.
			M	N	S	The 4 SAEs that occurred at this site were not submitted to the sponsor or IRB within 24 hours of the site becoming aware of the SAE. Reports to the sponsor were made 3, 9, 11, and 14 days after site became aware.
			M	N	S	17 screening ECGs were not dated by the PI to document prerandomization review. 9 original ECG tracings were not on file and for 8/9 subjects, the photocopy was not signed and dated.
			M	N	E	Subjects were "generally" randomized on the day of surgery; neither the IVRS acknowledgement nor the source document list the time of randomization so that preoperative randomization cannot be assured.
Mody India	N	Y	C	Y	S	Site safety reporting practices were deficient: There were 47 unreported AEs in 21 of 35 subject audited. Examples: chest

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
60010						pain/breathing difficulties, Tx 2U PRBCs, fever, hypertension, elevated amylase= 711 No source documentation for AE or Bleeding Event qualifying data. There were 3 unreported SAEs: chest infection requiring hospitalization; bedsore requiring hospitalization; hypotension & SOB requiring transfer.
			C	Y	S	**The EC used by the PI was formed at his request, the EC address is the PI's clinic, members include the PI, his wife and secretary, and the EC was not trained.**
			M	Y	E	**Study drug was not stored in permissible temperature range of 15-30^{o}C for 19 consecutive days, dropping to 10.2^{o}C each day.**
			M	Y	S	For 25 of 35 audited subjects, review of study documents was either not done or not done in a timely manner. This includes Progress Notes, lab reports, and ECGs
			m	Y	S	For 17 of 35 subjects, pre-study and/or concomitant medications were not recorded in the eCRF; most were Jonac suppository
			M	Y	S	For 12 of 25 subjects medical histories/conditions were not recorded in the eCRF or were documented in the CRF but not in the source documents. Examples include medication allergies, hypertension, diabetes, and bronchospasm.
			m	Y	B	There were discrepancies between the eCRF and site source documentation, including concomitant medications and ECGs interpreted as "Normal/Normal Variant" with the source document ECGs demonstrating abnormalities such as T wave depression, LBBB, and anterior wall ischemia.
			m	Y	B	Site source documents were deficient in content, missing and/or conflicting with other source documents. This included use of inappropriate correction medium and time of lab collection
			m	Y	E	For 34 of the 35 audited subjects who were randomized on the day of surgery, it could not be determined whether subjects were randomized postoperatively.
			m	Y	B	For 7 of the 35 audited subjects, there was no evidence of one (7 subjects) or 2 (2 subjects) protocol-required physical examinations.

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
Reddy India 60001	Y	N	C	Y	S	There were 3 unreported SAEs from this site: adenocarcinoma of the prostate; pyrexia requiring hospitalization, hospitalization for more than 12 hours for catheterization. There were 47 unreported AEs in 21 of 40 audited subjects. Examples include fever, elevated bilirubin. LBBB, decreased platelets, elevated ALT. There were discrepancies between source documentation and eCRF for AE start and stop dates and time. Inconsistencies in the level of source documentation for AE or Bleeding Event qualifying data.
			M	N	B	There were discrepancies between the eCRF and site source documentation for 32 of 40 subjects audited. Examples include time of venography, blood transfusions not recorded on the eCRF, time of study drug administration, and differences in vital signs.
			M	N	E	12 of 40 subjects audited were randomized postoperatively; deviation forms were present for 11 of the 12 subjects. For 7 additional subjects randomized on the day of surgery, it could not be determined whether randomization occurred postoperatively.
			m	N	E	Drug accountability procedures were inadequate and/or records were incomplete and/or discrepant with other subject source documentation in 8 of 40 subjects audited. Examples include discrepancies in whether a dose of study drug was administered and discrepancies in numbers of study drug doses returned.
			m	Y	B	Pre-study medical histories/conditions were not recorded in the eCRF for 6 of 40 subjects audited. Examples include hx of TKA and drug allergies.
			m	N	B	Source documents were deficient in content, missing, and/or conflicting with other documents. For all audited subjects, inappropriate correction techniqes were noted. For the majority of subjects, the study staff did not date signatures. Several subject records contained ECG thermal printouts which were faded such that they were illegible with no photocopies.
			m	N	B	Clinician review of study documents (progress notes, lab reports, ECG tracings) was untimely and/or missing for all 40 subjects. Clinical

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
						assessment of all abnormal local lab results could not be determined.
Sepulveda Mexico 32002	N	N	C	N	B	**The medical records of 10 subjects were missing from the site. Nursing notes, which include dosing entries, were missing for an additional 7 subjects.**
			C	N	S	1 of 33 subjects audited had only a blank, unsigned consent form in the study chart; this was one of the missing medical charts.
			M	Y	B	There were discrepancies between eCRF entries and medical chart information for 20 of the 33 subjects audited. Examples include surgery start and stop times, intraoperative blood loss, and venography date and time. For 1 subject a dosing worksheet was on file documenting some injection doses, but no tablets; no dosing data is entered in the eCRF.
			M	N	E	Differences were noted in number of tablets/injections returned vs number that should have been returned for 19 of 33 subjects audited. However, compliance was not outside the 80-100% allowed per protocol.
			M	N	E	**15 of the 33 subjects audited had source vs eCRF discrepancies pertaining to study drug administration noted, ranging from 1 to all doses, most = 2-3 doses.**
			M	N	S	Source documentation of AEs was inconsistent with eCRF entries or was missing qualifying data, including start and stop dates. There were 13 unreported AEs in 25 of 33 audited subjects. Examples include: edema, hematoma, wound infection, ALT/AST > 3X ULN.
			M	N	B	There were source documentation deficiencies and discrepancies relative to laboratory reports and other study procedures in 15 of 33 audited subjects. These include PI failure to review labs in a timely manner, failure of PI to sign/date lab reports, dating discrepancies, illegible ECGs on thermal paper. In addition, 1 subject withdrew consent after surgery; but per the eCRF, study procedures were performed through Visit 2/Day 1.
			m	N	E	For 9 of 33 subjects audited who were randomized on the day of surgery, it could not be determined from data at the site whether randomization occurred postoperatively.
			m	N	B	For 9 of the 33 subjects audited, medical history items were not recorded on

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
						the CRF. Examples include "cardiopathy", penicillin allergy, and knee replacement.
H. Shah India 60004	Y	N	M	Y	B	For 17 of 25 subjects use of one or more pre-study medication and/or concomitant medications were not recorded in the eCRF.
			M	N	S	Site safety reporting practices were deficient. There were 44 unreported AEs in 19 of 25 subjects at the site. Examples include probable LVH, possible MI, pitting edema, neutropenia, irregular heart beat. No source documentation for AE or Bleeding Event qualifying dat
			M	N	E	1 subject was randomized postoperatively
			M	N	B	No source documentation of protocol-required clinical VTE assessments by study staff for Visits 2, 3, 4, 5, and/or 6 for 11 of 25 subjects. No source documentation of protocol-required physical examinations by study staff for specific visit days (ranging from 1 to 4 visits) for 13 of 25 subjects.
			M	N	B	PI review of study documents, including progress notes, laboratory reports, ECG tracings was untimely and/or missing for 20 of 25 subjects.
			M	N	B	Study related procedures, assessments, and examinations were performed by 2 personnel not included on the Delegation of Duties Log. The ECGs were performed by an individual with no medical or scientific background and no documentation of training in ECG performance.
			M	N	B	Protocol Amendment 1 was submitted to the EC, but no approval letter is on file.
			m	Y	B	Pre-study medical conditions/histories were not recorded in the eCRF for 11 of the 25 subjects. Examples include allergic bronchitis, hypertension, drug allergy, and knee replacement.
			m	Y	B	There were discrepancies between the eCRF and site source documentation. Examples include time of venography, date of study visits, discharge date, time of outpatient study drug administration.
			m	Y	B	Site source documents were missing or deficient. For all subjects, inappropriate correction techniques were used.

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	[redacted] (b) (4) Rating C=Critical M=Major m=minor	Bayer or [redacted] (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
						For 18 of 25 subjects, source documentation was missing from subjects' hospital records, including Clinic First Consultation report, laboratory reports, randomization fax, and ECG tracing.
			m	N	S	4 subjects were randomized prior to documented clinical review of screening laboratory reports and/or ECG tracings.
			m	N	E	4 subjects were randomized on the day of surgery; based on site records, it could not be determined whether they were randomized postoperatively.
V. Shah India 60006	N	N	M	N	S	**According to the documented screening visit summary, a subinvestigator used language during the informed consent process which appears to be coercive. Documented language used includes "that the study drug was completely safe, that it was the best treatment currently available, that risks were minimal (same as any other surgery).**
			M	Y	S	Site safety reporting practices were deficient. There were 36 unreported AEs in 17 of 35 subjects audited at the site. Examples include fever, LE swelling, elevated ALT > 3X ULN. No source documentation for AE or Bleeding Event qualifying data such as seriousness, action taken with study drug, treatment severity, and relatedness. For 7 subjects there were discrepancies between the source documentation and the eCRF regarding AE start/stop dates, action taken, etc.
			M	N	E	**There were data discrepancies between the eCRF and site source documentation, including for study drug administration for 26 of 35 subjects audited (25 instance of discrepancies for study drug administration).** **For 3 subjects, source documentation and eCRF entries were changed months after an event, sometimes in response to a query from data management.**
			M	Y	B	Clinician review and/or completion of study documents (for example, progress notes, lab reports, ECG tracings) was untimely and/or missing.
			M	N	E	Coagulation parameter testing was done locally for 2 subjects, potentially

CI Location Site Number	DSI Site Data Reliable Overall Y/N	Study Monitor Failure Significant (Impacts primary efficacy or safety)	(b) (4) Rating C=Critical M=Major m=minor	Bayer or (b) (4) missed? Y/N ?=cannot asses	Impacts primary efficacy = E Safety = S B = Both	Detail*
						resulting in unblinding.
			m	N	E	Drug accountability procedures were inadequate and/or records were incomplete or discrepant with other subject source documentation. For 4 subjects expected versus returned study drug was discrepant, but did not fall outside the 80-100% allowed per protocol. [c]**There was missing source documentation for 1-6 days of study medication for 8 of 35 subjects.**
			m	N	B	Pre-study medical histories or conditions were not recorded in the eCRF for 22 of 35 subjects. Examples include knee replacement, osteoarthritis.
			m	N	B	**For all subjects, inappropriate correction techniques were used in hospital records.** 4 of 25 subjects had source documentation missing from the hospital chart, including copy of venography, central lab reports.
			m	Y	E	For 12 of 35 subjects, protocol violations were noted, including study medication given 5 minutes to 8 hours 42 minutes outside the window; 10 of 12 instances were less than an hour.

Bold = Finding impacting on the primary safety or efficacy outcome which results in inability to validate data from the site.
[a] *Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from this site as acceptable; see Section III.*
[b]Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from 4 of the 10 subjects in question at this site as acceptable; see Section III. Data is still considered unreliable.
[c]Evaluation of data submitted by Johnson & Johnson resulted in assessment of data from 1 of the 8 subjects in question at this site as acceptable; see Section III. Data is still considered unreliable.

APPENDIX 2

SUMMARY TABLE: DSI Analysis of Johnson & Johnson Response to August 2, 2010 Information Request

Study Site	J&J Response/Finding	DSI Assessment of J&J Response/Finding
Lenart, RECORD 1, Site 46002, Hungary: Study coordinators used logs to document drug	Study drug was prescribed by the PI on the "Fever sheet." Initials on Fever sheet indicate medication administration. 35 subject	Although some initials are noted on the "Fever sheet", th day/date and time of drug administration are not noted.

accountability and dosing for all subjects, but entries in the logs were not signed and dated/initialed; medications and infusions administered to the study subjects were recorded inconsistently; no documentation of subject training on injection techniques, dosing instructions, proper storage of study drug.	medication administration records (Fever sheets) were inspected, and of these 28 were initialed twice, 3 were initialed once, and 4 were not initialed. Training on injection technique/dosing/storage was routinely done verbally and documentation regarding this was not available.	Although the Study Coordinator's notebook containing information regarding study drug dispensation is supportive, this document is not a source document. The (b) (4) finding that study drug accountability and dosing log entries for all subjects were not signed and dated/initialed and that medication administration were recorded inconsistently is unchanged.
Porvaneckas, RECORD 1, Site 57001 Brazil: Study drug administration times were exactly the same of each of the 34 subjects audited; exact dosing times were not documented.	The logs for randomly selected patients confirmed the dose of investigational medicinal product (IMP), route of dispensing, and required time of dispensing by the physician. These entries were initialed by the physician and the nurse.	The nurse's initials are not accompanied by dates/times. The sponsor submitted the Hospital Operating Procedure which state that a nurse must make a notation if the medication is given more than 5 minutes for injection or 7 minutes for oral outside the prescribed window. Since there is no other source to verify that the medication was given at the prescribed time, the (b) (4) finding is unchanged.
Schwartsmann, RECORD 1, Site 50006: For all 35 subjects audited, documentation of study drug administration during the inpatient phase is captured only on progress notes as "administered dose of study 11354 medication per protocol at XXX [time]". It is not clear whether the tablet or syringe were administered, or both. In addition, 8 of 35 subjects audited lacked documentation of a single dose of study drug; 1 additional subject lacked documentation for Days 1-6.	Study drug administration during hospitalization was documented on the source data worksheet either by the study coordinator or by the study nurse, and entries were signed and dated. These data entries were identified and the appropriate source documents obtained.	The evidence submitted by the sponsor is sufficient to ensure that drug administration was appropriately documented.
Slappendel, RECORD 1, Site 30002, Netherlands: 10 of 35 subjects audited had drug accountability records which were incomplete and/or discrepant with other subject source documentation. In addition, no source documentation to support the date and time of the preoperative self administered injection of enoxaparin/placebo by the subjects or the date and time of the last outpatient dosing for all subjects.	Alternate source documents were identified to address drug accountability and outpatient dosing.	The additional information provided was adequate to provide evidence of drug administration for four subjects 300024054-153563, 300024054-153565, 300024059-153618, and 300024021-150856. However, the evidence presented for the remaining six subjects is not considered adequate.

Nafarrete, RECORD 2, Site 32005, Mexico: Study drug administration times were exactly the same for each subject for all subjects audited; exact times could not be documented.	Study drug administration is documented in the nurse's notes which are part of the medical charts indicating 8:00, 14:00, or 20:00, but not the exact time. This is routine practice in this hospital but not documented as such in a hospital policy.	No additional information was provided to provide reassurance of drug administration. No change in conclusions.
Ono, RECORD 2, Site 50005, Brazil: Documentation of study drug administration during the inpatient phase of the study was missing or deficient: 8 subject records contained very few notations that the study drug had been given, and the remaining 16 records contained none. Doses of study medication documented only on the SDW were not signed/initialed or dated, so it is unclear whether they are primary source entries.	Source documentation to support dosing of study drug for multiple subjects was identified and provided source data worksheets.	The entries on the source data worksheets were not routinely singed and dated. Therefore, they cannot be considered to be evidence of drug administration.
Brabants, RECORD 3, Site 28015, Belgium: The exact time of drug administration was rarely recorded on the inpatient medication administration for any of the 27 subjects – the times were recorded only on a grid with times of 0800, 1200, 1600, and 2000. Times of study drug administration frequently do not match the times noted on the inpatient medication administration sheets. In addition, the drug accountability logs provided by Bayer were not used by the study coordinator to record drug accountability. In addition, the study coordinator was unable to define a consistent primary source for many of the data points, including drug dosing, surgery start/times, and laboratory draw times. Please provide this information, if available.	No additional data were available.	No change in conclusions.
V. Shah, RECORD 4, Site 60006, India: Source documentation for 16 days of study drug medication was missing for 8 of 35 subjects.	Additional source documents supporting study drug administration were obtained from study drug dispensing logs, hospital file treatment sheets, nurse's notes, study coordinator's notes and post operative orders.	The additional information provided for the eight subjects is considered adequate for one subject. However, most or all of the information for the remaining 7 subjects in question did not provide documentation of most or all drug dispensation doses.

APPEARS THIS WAY ON ORIGINAL

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/s/

SUSAN D THOMPSON
05/24/2011

TEJASHRI S PUROHIT-SHETH
05/25/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022406

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Ortho McNeil Janssen
c/o Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 08869-0602

ATTENTION: Andrea F. Kollath, DVM
Director, Regulatory Affairs

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) dated July 22, 2008, received July 29, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Rivaroxaban Tablets, 10 mg.

We also refer to your February 25, 2011, correspondence, received February 25, 2011, requesting review of your proposed proprietary name, Xarelto. We have completed our review of the proposed proprietary name, Xarelto and have concluded that it is acceptable.

The proposed proprietary name, Xarelto, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your February 25, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Tyree Newman at (301) 796-3907.

Sincerely,
{See appended electronic signature page}
Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
05/12/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-406 **INFORMATION REQUEST**

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) Tablets.

We also refer to your December 30, 2010, submission, containing a Class 2 response to our May 27, 2009, action letter.

We are reviewing the Chemistry, Manufacturing, and Control section of your submission and have the following comments and information requests. We request a prompt written response by May 4, 2011, in order to continue our evaluation of your NDA.

Relating to DMF 21580 in support of Johnson & Johnson Pharmaceutical Research & Development's drug product application (NDA):

1. Your primary and secondary stability studies include the use of a matrix design for the different containers and closures and a bracketing approach for the number of tablets filled to support your proposed shelf life. Submit in a tabular format comparative evaluation of the containers/closures and fill volumes to support your matrix and bracketing design. Include comparative data for the container/closure composition, moisture vapor transmission rate, strengths, container size, container fill and other parameters critical to support the stability of your drug product.

2 Provide a complete comparison of the HDPE bottle configurations' (b) (4) per tablet to demonstrate package equivalence in the primary stability studies and to support the proposed marketed bottle configurations.

3. Submit data demonstrating that the hardness and water content changes observed during the stability studies do not affect the dissolution with a recommended dissolution acceptance criterion (Q = (b) (4) at 15 minutes).

4. Provide the correlation between [redacted] (b) (4) per tablet and hardness/water content change for each packaging configuration.

5. Clarify the temperature and humidity ranges used in the primary stability studies. Provide additional justification if the conditions for the long term stability studies are not the same as the controlled conditions mentioned in ICH Q1 (e.g. 25°C +/- 2°C/60%RH +/- 5%RH).

Relating to DMF 21592 in support of Johnson & Johnson Pharmaceutical Research & Development's drug product application (NDA):

1. The proposed release specifications for Rivaroxaban Film-Coated Tablets manufactured by Johnson & Johnson Janssen Ortho are inconsistent with the specifications used for Rivaroxaban Film-Coated Tablets in primary stability studies by Bayer HealthCare. Correct any inconsistencies and submit a single specification for both proposed manufacturing sites.

2. Skip lot testing for microbial purity is not acceptable. Revise accordingly.

3. Clarify the temperature and humidity ranges for the site specific stability studies, to demonstrate that the site specific stability data adequately support the proposed storage conditions. Provide additional justification if the conditions employed for the site specific stability studies are not the same as the controlled room temperature conditions mentioned in ICH Q1 (e.g. 25°C +/- 2°C/60%RH +/- 5%RH).

4. Provide justification for omitting hardness and water content in the proposed specifications for the drug product.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Health Project Manager, at (301) 796-4246.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
04/21/2011

From: Mesmer, Deborah
Sent: Thursday, April 21, 2011 9:42 AM
To: 'Kollath, Andrea [PRDUS]'
Cc: Lambert, Tu-Van
Subject: NDA 22-406- LOA

Dear Dr. Kollath,

As discussed in our phone conversation this morning, please submit to NDA 022406 a proper LOA for DMF 21592.

Sincerely,

Debbie Mesmer

Deborah Mesmer
Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)
Division of New Drug Quality Assessment (DNDQA1)
Food and Drug Administration
White Oak Building 21, Rm 1627
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

(301) 796-4023
deborah.mesmer@fda.hhs.gov

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, April 21, 2011 9:38 AM
To: Mesmer, Deborah
Subject: NDA 22-406

Dear Deborah,
e-mail as discussed.
Kind regards,
Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

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/s/

DEBORAH M MESMER
04/21/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-406 **INFORMATION REQUEST**

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) Tablets.

We also refer to your December 30, 2010 submission, containing a Class 2 response to our May 27, 2009 action letter.

We are reviewing the Chemistry, Manufacturing and Control - Biopharmaceutics section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

In light of the release data of the pilot and commercial batches, the Agency proposes the following in-vitro dissolution specification for both Bayer and Johnson & Johnson manufacturing facilities:

Q = (b) (4) **at 15 minutes** using the following dissolution methodology:

Apparatus	USP apparatus 2 (paddle)
Dissolution medium	900 mL acetate buffer pH 4.5 + 0.2 % SDS
Rotation speed	75 rpm
Analytical procedure	HPLC with UV/VIS detection or UV/VIS spectrophotometry Both analytical procedures lead to the same results and may thus be used interchangeably.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Health Project Manager, at (301) 796-4246.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
04/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

Please send immediately following the Filing/Planning meeting

TO:

CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor) **Marcus Cato, RPM, Division of Hematology Products**

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS
February 11, 2011		**NDA-022406**	(PLEASE CHECK OFF BELOW) **Resub/Class 2 (Labeling)**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
XARELTO™ (Rivaroxaban)	**Rush**	**Anticoagulant**	**June 3, 2011**

NAME OF FIRM:

J&J

PDUFA Date: **July 3, 2011**

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☒ PATIENT PACKAGE INSERT (PPI)
- ☒ CARTON/CONTAINER LABELING
- ☒ MEDICATION GUIDE
- ☒ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☒ ORIGINAL NDA/BLA
- ☐ IND
- ☐ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☒ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:
EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 **Global Submit:** \\CDSESUB1\EVSPROD\NDA022406\022406.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS: **NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review, provide comment and attend any related meetings (from your disciple perspective).**
EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 **Global Submit:** \\CDSESUB1\EVSPROD\NDA022406\022406.enx

Please contact Marcus Cato for any questions 301-796-3903

	Reviewer	Team Leader
Clinical Reviewer	**Lu, Min**	**Robie Suh, Kathy M**
Regulatory Project Manager	**Cato, Marcus**	**Jamison, Janet**

PDUFA Goal Date: **July 3, 2011**

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
☐ eMAIL ☐ HAND

Reference ID: 2904479

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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Pediatric and Maternal Health Staff (PMHS)	Marcus Cato, RPM, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 11, 2011		NDA-022406	Resubmission/Class 2	January 3, 2011

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
XARELTOTM (Rivaroxaban)	Rush	Anticoagulant	TBD

NAME OF FIRM: J&J

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTOTM (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review (labeling), provide comment and attend any related meetings (from your disciple perspective).
EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059
Global Submit: \\CDSESUB1\EVSPROD\NDA022406\022406.enx

Please contact Marcus Cato for any questions 301-796-3903

	Reviewer	Team Leader
Clinical Reviewer	Lu, Min	Robie Suh, Kathy M
Non-Clinical Reviewer	Chopra, Yash M	Saber, Haleh
Regulatory Project Manager	Cato, Marcus	Jamison, Janet
Clin Pharm Reviewer	Grillo, Joseph	Bullock, Julie

PDUFA Goal Date: July 3, 2011	
SIGNATURE OF REQUESTOR Marcus Cato	METHOD OF DELIVERY (Check one) ☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
Quantitative safety team in the Office of Biostatistics/through Mandi Yu

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Marcus Cato, RPM, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 11, 2011		**NDA-022406**	**Resubmission/Class 2**	**January 3, 2011**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
XARELTO™ (Rivaroxaban)	**Rush**	**Anticoagulant**	**March 30, 2011**

NAME OF FIRM: **J&J**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Resub/Class 2**

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review (the ROCKET study for liver safety evaluation and verification), provide comment and attend any related meetings (from your disciple perspective).

EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 **Global Submit:** \\CDSESUB1\EVSPROD\NDA022406\022406.enx

Please contact Marcus Cato for any questions 301-796-3903

	Reviewer	Team Leader
Clinical Reviewer	**Lu, Min**	**Robie Suh, Kathy M**
Non-Clinical Reviewer	**Chopra, Yash M**	**Saber, Haleh**
Regulatory Project Manager	**Cato, Marcus**	**Jamison, Janet**
Clin.Pharm. Reviewer	**Grillo, Joseph**	**Bullock, Julie**

PDUFA Goal Date: **July 3, 2011**

SIGNATURE OF REQUESTOR
Marcus Cato

METHOD OF DELIVERY (Check one)
☒ DFS ☒ EMAIL ☒ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
GOOD CLINICAL PRACTICES BRANCH II
OC/CDER/OC/DSI/GCPBII/

FROM (*Name, Office/Division, and Phone Number of Requestor*): Marcus Cato, RPM, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 11, 2011		**NDA-022406**	**Resubmission/Class 2**	**January 3, 2011**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
XARELTO™ (Rivaroxaban)	**Rush**	**Anticoagulant**	**March 30, 2011**

NAME OF FIRM: **J&J**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Resub/Class 2**

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review, provide comment and attend any related meetings (from your disciple perspective).

EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 **Global Submit:** \\CDSESUB1\EVSPROD\NDA022406\022406.enx

Please contact Marcus Cato for any questions 301-796-3903

	Reviewer	Team Leader
Clinical Reviewer	**Lu, Min**	**Robie Suh, Kathy M**
Non-Clinical Reviewer	**Chopra, Yash M**	**Saber, Haleh**
Regulatory Project Manager	**Cato, Marcus**	**Jamison, Janet**
Clin.Pharm. Reviewer	**Grillo, Joseph**	**Bullock, Julie**

PDUFA Goal Date: **July 3, 2011**

SIGNATURE OF REQUESTOR
Marcus Cato

METHOD OF DELIVERY (Check one)
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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
DIVISION OF RISK MANAGEMENT (OC/CDER/OSE/DRISK/)	Marcus Cato, RPM, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 11, 2011		**NDA-022406**	**Resubmission/Class 2**	**January 3, 2011**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
XARELTO™ (Rivaroxaban)	**Rush**	**Anticoagulant**	**March 30, 2011**

NAME OF FIRM: **J&J**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Resub/Class 2**

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review (for possible liver monitoring), provide comment and attend any related meetings (from your disciple perspective).

EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 **Global Submit:** \\CDSESUB1\EVSPROD\NDA022406\022406.enx

Please contact Marcus Cato for any questions 301-796-3903

	Reviewer	Team Leader
Clinical Reviewer	**Lu, Min**	**Robie Suh, Kathy M**
Non-Clinical Reviewer	**Chopra, Yash M**	**Saber, Haleh**
Regulatory Project Manager	**Cato, Marcus**	**Jamison, Janet**
Clin.Pharm. Reviewer	**Grillo, Joseph**	**Bullock, Julie**

PDUFA Goal Date: **July 3, 2011**

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
DIVISION OF MEDICATION ERROR PREVENTION & ANALYSIS (OC/CDER/OSE/DMEPA/)	Marcus Cato, RPM, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 11, 2011		**NDA-022406**	**Resubmission/Class 2**	**January 3, 2011**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
XARELTO™ (Rivaroxaban)	**Rush**	**Anticoagulant**	**March 30, 2011**

NAME OF FIRM: **J&J**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Resub/Class 2**

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review (Labeling/Trade Name), provide comment and attend any related meetings (from your disciple perspective).

EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 **Global Submit:** \\CDSESUB1\EVSPROD\NDA022406\022406.enx

Please contact Marcus Cato for any questions 301-796-3903

	Reviewer	Team Leader
Clinical Reviewer	**Lu, Min**	**Robie Suh, Kathy M**
Non-Clinical Reviewer	**Chopra, Yash M**	**Saber, Haleh**
Regulatory Project Manager	**Cato, Marcus**	**Jamison, Janet**
Clin.Pharm. Reviewer	**Grillo, Joseph**	**Bullock, Julie**

PDUFA Goal Date: **July 3, 2011**

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Marcus Cato	☒ DFS ☒ EMAIL ☒ MAIL ☐ HAND
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/s/

MARCUS A CATO
02/11/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:
DIVISION OF EPIDEMIOLOGY (OC/CDER/OSE/DEPI/): c/o Dr. John Senior, Dr. Kate Gelperin

FROM (*Name, Office/Division, and Phone Number of Requestor*): Marcus Cato, RPM, Division of Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 11, 2011		**NDA-022406**	**Resubmission/Class 2**	**January 3, 2011**

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
XARELTO™ (Rivaroxaban)	**Rush**	**Anticoagulant**	**March 30, 2011**

NAME OF FIRM: **J&J**

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
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- ☐ PRE-NDA MEETING
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: **Resub/Class 2**

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

NDA-022406 (SDN70) Is a Class 2 Resubmission of XARELTO™ (Rivaroxaban) Tablets to address deficiencies in the May 27, 2009, DMIHP complete response letter. Please review data related to liver toxicity. provide comment and attend any related meetings (from your disciple perspective).

EDR Location: \\CDSESUB1\EVSPROD\NDA022406\0059 **Global Submit:** \\CDSESUB1\EVSPROD\NDA022406\022406.enx

Please contact Marcus Cato for any questions 301-796-3903

	Reviewer	Team Leader
Clinical Reviewer	**Lu, Min**	**Robie Suh, Kathy M**
Non-Clinical Reviewer	**Chopra, Yash M**	**Saber, Haleh**
Regulatory Project Manager	**Cato, Marcus**	**Jamison, Janet**
Clin.Pharm. Reviewer	**Grillo, Joseph**	**Bullock, Julie**

PDUFA Goal Date: **July 3, 2011**

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Marcus Cato	☒ DFS ☒ EMAIL ☒ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARCUS A CATO
02/11/2011

Cato, Marcus

From: Cato, Marcus
Sent: Thursday, January 27, 2011 11:36 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request
Importance: High
Attachments: eDISHdataRequirement.xls; narrative_enter_by_hand.sas

Dear Andrea,

We would like you to submit clinical narratives in a SAS data set and send to us by direct mail (FedEx or UPS), rather than to the EDR system.

Attached are:

1. An Excel file detailing data requirements including why and how to create reviewable clinical narratives by your company's physicians (not by computer technicians and no data dumps to the Agency)
2. A SAS program that enables your SAS program to create the narratives we want.

The files can be sent to me at the address below.

Marcus Cato
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 5241
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

We are requesting a response by **12:00 PM Friday February 4, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

11 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MARCUS A CATO
02/05/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22406

ACKNOWLEDGE – CLASS 2 RESPONSE

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

We acknowledge receipt on January 3, 2011, of your December 30, 2010, resubmission of your new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) Tablets.

We consider this a complete, Class 2 response to our May 27, 2009, action letter. Therefore, the user fee goal date is July 3, 2011.

If you have any questions, call me at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARCUS A CATO
01/14/2011

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE:	October 14, 2010 – April 15, 2011
APPLICATION NUMBER:	NDA 22406

BETWEEN:

Name:	Andrea Kollath, DVM, Global Regulatory Affairs
e-mail:	akollath@its.jnj.com
Representing:	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

AND

Name:	Marcus Cato, M.B.A., Regulatory Project Manager Division of Hematology Products Office of Oncology Drug Products Center for Drug Evaluation and Research

SUBJECT: Information Requests/General Correspondence

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, April 15, 2011 4:44 PM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Hi Marcus,
Regarding these questions, we wanted to know if the Reviewer was aware of the responses sent to CardioRenal Division ? On Feb 28 Sequence #23- an updated combined dataset was sent to CardioRenal. Does the Reviewer have access to that database?
Do the NDA 22-406 Reviewers have access to the responses sent to CardioRenal in general?
Thanks
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, April 14, 2011 1:29 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 Information Request

Dear Andrea,
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XARELTO (rivaroxaban) .

We are reviewing the statistical section in your submission and have the attached comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.
We are requesting a response by **12:00 PM Monday April 25, 2011**.
Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**
Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, April 14, 2011 1:34 PM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Hi Marcus,
I will review this with our statisticians right away.
Kind regards,
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, April 14, 2011 1:29 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 Information Request

Dear Andrea,
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XARELTO (rivaroxaban) .

We are reviewing the statistical section in your submission and have the attached comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.
We are requesting a response by **12:00 PM Monday April 25, 2011**.
Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**
Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Thursday, April 14, 2011 1:23 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request

Attachments: Liver Safety Review Issues v2.doc

Dear Andrea,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We are reviewing the statistical section in your submission and have the attached comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Liver Safety Review Issues v2....

We are requesting a response by **12:00 PM Monday April 25, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Thursday, April 14, 2011 1:29 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request

Attachments: Liver Safety Review Issues v2.doc

Dear Andrea,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for XARELTO (rivaroxaban) .

We are reviewing the statistical section in your submission and have the attached comments and information requests. We request a prompt written response in order to continue our evaluation

of your NDA.

Liver Safety Review Issues v2....

We are requesting a response by **12:00 PM Monday April 25, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, April 06, 2011 10:12 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 202439 seq 0036

Hi Andrea,

Thanks, will do

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Tuesday, April 05, 2011 11:26 PM
To: Cato, Marcus
Subject: NDA 202439 seq 0036

Dear Marcus,

The attached cover letter was filed with a submission to the Division of Cardiovascular and Renal products with a cc to the Division of Hematology.

If you have any questions please let me know.

Best regards

Andrea

<<...>>

Date Dispatched: 5 April 2011

E-Sub Server Path/Gateway Receipt and Core ID Information (one for each submission/sequence):

Note: The dispatch notification process has been enhanced to decrease the size of emails and increase efficiencies. All Gateway dispatch notices now note the Core ID Number which is found within the Gateway receipt. This information is also included within the WRAT entry of Gateway submissions. Please contact any US GSO Publisher with questions regarding this update.

Archive\eCTD\NDA\202439\0036\m1\us

Cato, Marcus

From: Cato, Marcus
Sent: Thursday, March 31, 2011 11:40 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 PUDUFA action date

Hi Andrea,

Sorry for the delay in reply, the action date is technically July 3rd 2011. It may be best to treat the action date as July 1st.
Thanks
~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, March 28, 2011 10:58 AM
To: Cato, Marcus
Subject: NDA 22-406 PUDUFA action date

Hi Marcus
We have a question on when the action date for this current application is. We submitted our complete response to FDA on Dec 30th, the 31st was a holiday, and the FDA receipt is from Jan 3rd. The action date is the 3rd of July, which is a Sunday, Monday is July 4th holiday, so when can we expect a response? July 1st or July 5th?
It may seem trivial but it has an impact on the company.
Thank you and Kind regards
Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, March 28, 2011 10:58 AM
To: Cato, Marcus
Subject: NDA 22-406 PUDUFA action date

Hi Marcus
We have a question on when the action date for this current application is. We submitted our complete response to FDA on Dec 30th, the 31st was a holiday, and the FDA receipt is from Jan 3rd. The action date is the 3rd of July, which is a Sunday, Monday is July 4th holiday, so when can we expect a response? July 1st or July 5th?
It may seem trivial but it has an impact on the company.
Thank you and Kind regards
Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, February 28, 2011 1:03 PM
To: Kang, Sue; Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Attachments: ORS_Cover_Letter_Proprietory Name Request_ _2_.pdf; ORS NDA request tradename review Feb 25 2011.pdf; emfalert.txt


ORS_Cover_Letter _Proprietory N...


ORS NDA request tradename revi...


emfalert.txt (659 B)

Dear Ms. Kang and Marcus,

Attached please find a copy of the cover letter and the request for proprietary name review submitted through Gateway on Friday February 25, 2011 to the Division of Medication Error Prevention and Analysis.

If you have any questions please contact me any time.
Kind regards,

Andrea

From: Kollath, Andrea [PRDUS]
Sent: Friday, February 25, 2011 11:46 AM
To: Kang, Sue
Cc: Marcus.Cato@fda.hhs.gov
Subject: RE: NDA 22406 (rivaroxaban)

Dear Ms. Kang,

I will be send out the letter today or Monday.
I can cc you on the Gateway submission cover letter and attachment.
We recently send a similar request for the new NDA submitted to Division of Cardiovascular and Renal Products. I will use the same format and information. See below.
Best regards,
Andrea

“REQUEST FOR PROPRIETARY NAME REVIEW” with regard to the New Drug Application (NDA) 202,439 for rivaroxaban, an oral anticoagulant, which is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]
Sent: Friday, February 25, 2011 10:47 AM
To: Kollath, Andrea [PRDUS]
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Dr. Kollath,

Can you provide me with an update as to when you plan on submitting your request to review a proprietary name?

Kind regards,
Sue Kang
Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 3475
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel: 301-796-4216
Email: sue.kang@fda.hhs.gov

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Tuesday, February 15, 2011 3:53 PM
To: Kang, Sue
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)
Dear Sue,
We will provide the requested amendment.
Thank you.
Andrea

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]
Sent: Tuesday, February 15, 2011 3:37 PM
To: Kollath, Andrea [PRDUS]
Cc: Cato, Marcus
Subject: NDA 22406 (rivaroxaban)

Dr. Kollath,

As a follow-up to our phone conversation this afternoon regarding your proprietary name review, you will need to submit an amendment to your NDA and code this amendment as a request for review of a proprietary name. This submission will trigger a 90 day review clock. In your submission, if no product characteristics have changed since the original NDA submission, you may reference the proprietary name information from your original NDA submission.

If you have any questions or comments, please do not hesitate to contact me.

Kind regards,

Sue Kang
Project Manager

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 3475
10903 New Hampshire Avenue
Silver Spring, MD 20993

Tel: 301-796-4216
Email: sue.kang@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Monday, February 28, 2011 12:52 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

ok, Thanks
~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, February 28, 2011 12:35 PM
To: Cato, Marcus
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

Hi Marcus.
Correct. We are planning on submitting the clinical narratives around the end of this week to Division of Cardiovascular and Renal Products and a copy of the cover letter to you.

Is that sufficient?
Kind regards
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Monday, February 28, 2011 8:51 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

Hi Andrea,

Thanks. Were you all still planning to submit clinical narratives in a SAS (version 9.2) data by direct mail (FedEx or UPS). I heard a few different things, last I heard was you were in early March?
Thanks
~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Friday, February 25, 2011 4:43 PM
To: Cato, Marcus
Subject: Response to IR on eDISH datasets for ROCKET AF study
Dear Marcus,

Attached please find your copy of the cover letter sent to Division of Cardiovascular and Renal Products today with the response to the IR for eDISH datasets for the ROCKET AF study.

If you have any questions please contact me.
Kind regards
Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, February 28, 2011 12:35 PM
To: Cato, Marcus
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

Attachments: emfalert.txt

emfalert.txt (659 B)

Hi Marcus.
Correct. We are planning on submitting the clinical narratives around the end of this week to Division of Cardiovascular and Renal Products and a copy of the cover letter to you.

Is that sufficient?
Kind regards
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Monday, February 28, 2011 8:51 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

Hi Andrea,

Thanks. Were you all still planning to submit clinical narratives in a SAS (version 9.2) data by direct mail (FedEx or UPS). I heard a few different things, last I heard was you were in early March?
Thanks
~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Friday, February 25, 2011 4:43 PM
To: Cato, Marcus
Subject: Response to IR on eDISH datasets for ROCKET AF study
Dear Marcus,

Attached please find your copy of the cover letter sent to Division of Cardiovascular and Renal Products today with the response to the IR for eDISH datasets for the ROCKET AF study.

Cato, Marcus

From: Cato, Marcus
Sent: Monday, February 28, 2011 8:51 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: Response to IR on eDISH datasets for ROCKET AF study

Hi Andrea,

Thanks. Were you all still planning to submit clinical narratives in a SAS (version 9.2) data by direct mail (FedEx or UPS). I heard a few different things, last I heard was you were in early March?
Thanks
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Kind regards
Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, February 25, 2011 4:43 PM
To: Cato, Marcus
Subject: Response to IR on eDISH datasets for ROCKET AF study

Attachments: CL response to IR eDISH datasets Feb 25 2011.pdf

CL response to IR eDISH datase...

Dear Marcus,

Attached please find your copy of the cover letter sent to Division of Cardiovascular and Renal Products today with the response to the IR for eDISH datasets for the ROCKET AF study.

If you have any questions please contact me.
Kind regards
Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, February 25, 2011 11:46 AM
To: Kang, Sue
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Dear Ms. Kang,

I will be send out the letter today or Monday.
I can cc you on the Gateway submission cover letter and attachment.
We recently send a similar request for the new NDA submitted to Division of Cardiovascular and Renal Products. I will use the same format and information. See below.
Best regards,
Andrea

"REQUEST FOR PROPRIETARY NAME REVIEW" with regard to the New Drug Application (NDA) 202,439 for rivaroxaban, an oral anticoagulant, which is indicated for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]
Sent: Friday, February 25, 2011 10:47 AM
To: Kollath, Andrea [PRDUS]
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Dr. Kollath,

Can you provide me with an update as to when you plan on submitting your request to review a proprietary name?

Kind regards,
Sue Kang
Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 3475
10903 New Hampshire Avenue
Silver Spring, MD 20993
Tel: 301-796-4216
Email: sue.kang@fda.hhs.gov

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Tuesday, February 15, 2011 3:53 PM
To: Kang, Sue
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)
Dear Sue,
We will provide the requested amendment.
Thank you.
Andrea

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]
Sent: Tuesday, February 15, 2011 3:37 PM
To: Kollath, Andrea [PRDUS]
Cc: Cato, Marcus
Subject: NDA 22406 (rivaroxaban)

Dr. Kollath,

As a follow-up to our phone conversation this afternoon regarding your proprietary name review, you will need to submit an amendment to your NDA and code this amendment as a request for review of a proprietary name. This submission will trigger a 90 day review clock. In your submission, if no product characteristics have changed since the original NDA submission, you may reference the proprietary name information from your original NDA submission.

If you have any questions or comments, please do not hesitate to contact me.

Kind regards,

Sue Kang
Project Manager

Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 3475
10903 New Hampshire Avenue
Silver Spring, MD 20993

Tel: 301-796-4216
Email: sue.kang@fda.hhs.gov

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Tuesday, February 15, 2011 3:53 PM
To: Kang, Sue
Cc: Cato, Marcus
Subject: RE: NDA 22406 (rivaroxaban)

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Dear Sue,
We will provide the requested amendment.
Thank you.
Andrea

From: Kang, Sue [mailto:Sue.Kang@fda.hhs.gov]
Sent: Tuesday, February 15, 2011 3:37 PM
To: Kollath, Andrea [PRDUS]
Cc: Cato, Marcus
Subject: NDA 22406 (rivaroxaban)

Dr. Kollath,

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If you have any questions or comments, please do not hesitate to contact me.

Kind regards,

Sue Kang
Project Manager

Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg. 22; Room 3475
10903 New Hampshire Avenue
Silver Spring, MD 20993

Tel: 301-796-4216
Email: sue.kang@fda.hhs.gov

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, February 07, 2011 11:36 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Hi Marcus,
No problem, just wanted to make sure.
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Monday, February 07, 2011 11:12 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22406 Information Request

Hi Andrea,

It is for Rivaroxaban, forgive me it was a typographical error...

Thanks
~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, February 07, 2011 8:22 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request
Hi Marcus,
I am confirming receipt of this message and I have a question. I am wondering why you quoted "section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection."
? This is for Rivaroxaban? An oral tablet.
Kind regards
Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Saturday, February 05, 2011 2:04 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 Information Request

Dear Andrea,
Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We are reviewing the clinical pharmacology section in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation
of your NDA.

1. Submit the study report, control streams and datasets used for the simulations to assess appropriateness of 5 mg rivaroxaban dose in subjects receiving strong inhibitors of both CYP3A4 and P-gP. All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt).

2. Your document "Rivaroxaban: Complete Response to FDA Letter of May 27, 2009" on Page 27 under "Patients with Child-Pugh class B hepatic impairment without coagulopathy" states that: "Furthermore, PT both at baseline and during treatment with rivaroxaban was more pronounced in Child Pugh class B subjects due to the underlying hepatic disease which impairs the ability of the liver to synthesize clotting factors. This led to a increased pharmacodynamic response and a steeper PK/PD relationship between rivaroxaban plasma concentrations and PT in Child Pugh class B patients (7.8 seconds/(100 µg/L) for C-P class B patients versus 3.1 seconds/(100 µg/L) for healthy subjects with normal hepatic function)."

Submit the data and report to support these findings or direct us to the document that provides more detail about these findings.

We are requesting a response by **12:00 PM Friday February 18, 2011**.
Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**
Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Saturday, February 05, 2011 2:04 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request

Dear Andrea,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Heparin Sodium Injection.

We are reviewing the clinical pharmacology section in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation

of your NDA.

1. Submit the study report, control streams and datasets used for the simulations to assess appropriateness of 5 mg rivaroxaban dose in subjects receiving strong inhibitors of both CYP3A4 and P-gP. All datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt).

2. Your document "Rivaroxaban: Complete Response to FDA Letter of May 27, 2009" on Page 27 under "Patients with Child-Pugh class B hepatic impairment without coagulopathy" states that: "Furthermore, PT both at baseline and during treatment with rivaroxaban was more pronounced in Child Pugh class B subjects due to the underlying hepatic disease which impairs the ability of the liver to synthesize clotting factors. This led to a increased pharmacodynamic response and a steeper PK/PD relationship between rivaroxaban plasma concentrations and PT in Child Pugh class B patients (7.8 seconds/(100 µg/L) for C-P class B patients versus 3.1 seconds/(100 µg/L) for healthy subjects with normal hepatic function)."

Submit the data and report to support these findings or direct us to the document that provides more detail about these findings.

We are requesting a response by **12:00 PM Friday February 18, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

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(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, March 16, 2011 4:44 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request

Dear Andrea,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

We are reviewing the clinical section in your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation

of your NDA.

1. Provide a summary of the incidence of ischemic stroke during on and off (within 30 days) treatment period in each of following studies: Rocket, J-Rocket, Einstein DVT, PE, and Extension, Atlas ACS Timi 46, 11223, and 11528.

2. Provide a summary of clinical outcomes of patients who had hepatic disorder adverse events leading to permanent study drug discontinuation in each of following studies: Rocket, J-Rocket, and Einstein DVT, PE, and Extension.

We are requesting a response by **12:00 PM Friday March 25, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, February 03, 2011 3:03 PM
To: Cato, Marcus
Subject: Telecon Feb 4 2011 3:30 to 4 PM

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Hi Marcus,
We are available for the telecon at this time.

Please use this call in number:

North American Dial-In Number: **(888) 627-7005**
Conference Code: **619833** #

Kind regards
Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202, PO Box 300
Raritan NJ 08869
phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Cato, Marcus
Sent: Monday, January 31, 2011 10:32 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22406 Information Request

Hi Andrea,

Will share with the team and get back to you.

Thanks

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, January 31, 2011 10:23 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Dear Marcus,

We met with our team on Friday and are hoping we have a better understanding of what you are asking for.

The e-Dish datasets for the ROCKET study can be provided within the next few days.

The narratives which are in the HEAC packets were manually generated for the HEAC members to review and therefore cannot be provided in SAS program.

Local lab values which were relevant were included in the narratives.

Again, if this is not what you were asking please contact me.

Best regards

Andrea

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To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22406 Information Request

Hi Andrea,

Yes. we were able to find the narratives. We would like you to clarify if the submitted ISLS has included LFTs from local labs in all completed phase 3 studies (2 ROCKET studies and 2 EINSTEIN studies) in the safety analysis including HEAC evaluations.

Thanks

~Marcus

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Hi Marcus,

We have a question.

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Kind regards,

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 27, 2011 11:36 AM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 Information Request
Importance: High

Dear Andrea,

We would like you to submit clinical narratives in a SAS data set and send to us by direct mail (FedEx or UPS), rather than to the EDR system.

Attached are:

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2. A SAS program that enables your SAS program to create the narratives we want.

The files can be sent to me at the address below.

Marcus Cato

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22, Room: 5241

10903 New Hampshire Avenue

Silver Spring, Maryland 20903

We are requesting a response by **12:00 PM Friday February 4, 2011**.

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Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, January 31, 2011 10:31 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Hi Marcus,

No problem,

Please the latest message from today.

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Monday, January 31, 2011 10:29 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22406 Information Request

My apologies, I wanted to set something up by was not able to on Friday (also did not see this e-mail). I will touch base with the team and get back with you

Thanks

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Friday, January 28, 2011 2:36 PM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Hi Marcus

I'm meeting with our response team at 3:30 PM today and if we had some clarification by then it would be really helpful.

If not then maybe you and I can talk later today?

Thanks

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From: Kollath, Andrea [PRDUS]
Sent: Thursday, January 27, 2011 4:01 PM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Hi Marcus

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Let me take a stab at the current questions I have received.

1) Regarding the original request you responded that yes- meaning the request is specific to liver-related narratives. Is this correct?

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Thank you and Kind regards

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Attachments: emfinfo.txt

emfinfo.txt (582 B)

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Cato, Marcus

From: Cato, Marcus
Sent: Thursday, January 27, 2011 11:53 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22406 Information Request

FYI - the request is to create a version 9 SAS data set for the narratives.

Thanks

~Marcus

From: Cato, Marcus
Sent: Thursday, January 27, 2011 11:36 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request
Importance: High

Dear Andrea,

We would like you to submit clinical narratives in a SAS data set and send to us by direct mail (FedEx or UPS), rather than to the EDR system.

Attached are:

1. An Excel file detailing data requirements including why and how to create reviewable clinical narratives by your company's physicians (not by computer technicians and no data dumps to the Agency)
2. A SAS program that enables your SAS program to create the narratives we want.

The files can be sent to me at the address below.

Marcus Cato

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22, Room: 5241

10903 New Hampshire Avenue

Silver Spring, Maryland 20903

We are requesting a response by **12:00 PM Friday February 4, 2011**.

Feel free to contact me directly, should you have any questions. **Please confirm receipt of this message**

Warmly,

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-3903 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, January 27, 2011 11:44 AM
To: Cato, Marcus
Subject: RE: NDA 22406 Information Request

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Hi Marcus,

I have received the request and we will start on this.

Kind regards,

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 27, 2011 11:36 AM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22406 Information Request
Importance: High

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To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22406 Information Request

Importance: High

Attachments: eDISHdataRequirement.xls; narrative_enter_by_hand.sas


eDISHdataRequirement.xls (37 K...


narrative_enter_by_hand.sas (6...

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From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, January 27, 2011 11:32 AM
To: Cato, Marcus
Subject: RE: NDA 22-406 Complete Response location of HEAC Packets

Attachments: emfalert.txt

emfalert.txt (659 B)

Hi Marcus,

Thanks for the advance notice. Just let us know what you need and we are happy to help.

Kind regards

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 27, 2011 11:24 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 Complete Response location of HEAC Packets

Hi Andrea,

Sorry for the delay in response (i believe the review team is still sorting through the submission) the information was helpful, however we will likely have additional requests in the near future.

Thanks

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From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, January 24, 2011 9:15 AM
To: Cato, Marcus
Subject: NDA 22-406 Complete Response location of HEAC Packets

Hi Marcus,

I just want to make sure that the information I sent was helpful or not. Has the Reviewer been able to locate the HEAC packets of information including the narratives?

Kind regards

Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

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akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Tuesday, January 18, 2011 12:17 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Attachments: Response to FDA Q Jan 11 2011 on location of HEAC Packets_3_.pdf; emfinfo.txt


Response to FDA Q Jan 11 2011 ... emfinfo.txt (582 B)

Hi Marcus,

Attached please see a list of the detailed location for the Hepatic Assessment Committee (HEAC) packets. Please note the HEAC packets include the patient narratives, the evaluation pages by the HEAC members and the patient profiles as well as the CIOMS.

If you have any questions please contact me.

Best regards

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 13, 2011 3:58 PM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
Importance: High

Hi Andrea

Our reviewer was unable to locate the patient narratives/CRFs based on the pages from the table. As you have submitted many separated PDF files. Could you please include specific names of files and pages for patient narratives, CRFs, and HPAC assessment in the table below.

Warmly,

~Marcus

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Cases of interest are defined as “at least 2 possible or higher HEAC causality assessments”

Study

Rivaroxaban

Comparator

Total

Source

ROCKET AF 11630

75

76

151

ISLS page 130

All cases located in ROCKET CSR Appendix 4

J-ROCKET 12620

9

5

14

ISLS page 170

All cases located in HEAC packets for J-ROCKET

EINSTEIN 11702 (DVT)

8

12

20

ISLS page 193

All cases located in EINSTEIN DVT CSR/MRR Appendix 16.4.1.3

EINSTEIN Extension (11899)

1

0

1

ISLS page 210

All cases located in EINSTEIN Ext CSR/MRR Appendix 16.4.1.3 and 16.4.1.4

EINSTEIN PE (11702)

(ongoing but open-label)

9

6

15

ISLS page 296

Only 2 cases of interest in ISLS Appendix 7.1.1.5

(other cases not included as this is a ongoing study)

TOTAL

102

99

201

ISLS: pages 64 and 65

ATLAS ACS 2 TIMI 51

Please note that ATLAS ACS 2 TIMI 51 study 13194 is not unblinded and therefore we do not know the number of rivaroxaban and comparator cases. There were a total of 18 subjects with ALT >3xULN and total bilirubin >2xULN concurrently and/or non-concurrently at any time in the study (see Table ISLS1.4 and Table ISLS1.3 in Appendix 7.1.2.1). (page 303 of the ISLS)

The HEAC packets are available in App 7.1.2.5 (four cases of interest)

-

Spontaneous reports

A total of 22 cases of interest were reviewed by HEAC. HEAC packets sent for review and the HEAC reviewer clinical evaluation forms and narratives for cases in Table 8.2.-5 can be found in Appendix 8.2.1.

-

If it would be helpful for us to meet with the Reviewer and walk through the location of any of the data

we would be happy to do so.

Let me know if there are any other questions.

Best regards

Andrea

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Sent: Tuesday, January 11, 2011 9:00 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
Importance: High

Hi Andrea,

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Our reviewer was unable to find all the information in the submission. She could only see CRFs for cases (only 20 cases)of the combined ALT>3xULN with total bilirubin >2x ULN cases with at least 2 possible or higher HEAC causality assessments from the Phase 3 clinical program in the submission.

Please submit this information or let us know the location if you have submitted.

Warmly

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, January 06, 2011 12:56 PM
To: Cato, Marcus
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Dear Marcus,

Please note that in the Sponsor Complete response all liver-related safety information is provided in a separate document, the Integrated Summary of Liver Safety (ISLS) which is located in Mod 5.3.5.3.

The *datasets* for the ISLS are provided to FDA in *NDA 202439*, submitted to the Cardio Renal Division yesterday January 5th for the indication of prevention of stroke and non CNS systemic embolism in patients with non-valvular atrial fibrillation.

If you have any questions regarding the ISLS datasets please contact me.

Kind regards

Andrea

From: Kollath, Andrea [PRDUS]
Sent: Monday, January 03, 2011 11:18 AM
To: 'Cato, Marcus'; susan.thompson1@fda.hhs.gov
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response

Dear Dr. Thompson and Marcus,

Happy New Year to both of you.

Attached please find the cover letter of the sponsor complete response submitted Dec 30th last week.

Marcus,

If you have any questions regarding the submission please contact me.

Kind regards

Andrea

Andrea Kollath, DVM,
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

From: Kollath, Andrea [PRDUS]
Sent: Wednesday, December 29, 2010 11:21 AM
To: Cato, Marcus
Subject: NDA 22-406 rivaroxaban Sponsor Complete Response

Dear Marcus,

Happy Holidays to you!

I wanted to let you know we are providing our sponsor complete response on December 30th to the FDA action letter received in May of 2009 for XARELTOÒ (rivaroxaban) for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.

I will send you a copy of the cover letter.

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Cato, Marcus

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Sent: Thursday, January 13, 2011 4:24 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

ok

Thanks

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Hi Marcus,

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Source

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ISLS page 130

All cases located in ROCKET CSR Appendix 4

J-ROCKET 12620

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ISLS page 170

All cases located in HEAC packets for J-ROCKET

EINSTEIN 11702 (DVT)

8

12

20

ISLS page 193

All cases located in EINSTEIN DVT CSR/MRR Appendix 16.4.1.3

EINSTEIN Extension (11899)

1

0

1

ISLS page 210

All cases located in EINSTEIN Ext CSR/MRR Appendix 16.4.1.3 and 16.4.1.4

EINSTEIN PE (11702)

(ongoing but open-label)

9

6

15

ISLS page 296

Only 2 cases of interest in ISLS Appendix 7.1.1.5

(other cases not included as this is a ongoing study)

TOTAL

102

99

201

ISLS: pages 64 and 65

ATLAS ACS 2 TIMI 51

Please note that ATLAS ACS 2 TIMI 51 study 13194 is not unblinded and therefore we do not know the number of rivaroxaban and comparator cases. There were a total of 18 subjects with ALT >3xULN and total bilirubin >2xULN concurrently and/or non-concurrently at any time in the study (see Table ISLS1.4 and Table ISLS1.3 in Appendix 7.1.2.1). (page 303 of the ISLS)

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Importance: High

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EINSTEIN Extension (11899)

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ISLS page 210

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(ongoing but open-label)

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ISLS page 296

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ISLS: pages 64 and 65

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PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301) 796-7550 and return it to us by mail at WO22 RM5241 HFD-160 10903 New Hampshire Ave., Silver Spring, MD 20903. Thank you.

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Dear Marcus,

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I wanted to let you know we are providing our sponsor complete response on December 30th to the FDA action letter received in May of 2009 for XARELTO® (rivaroxaban) for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip replacement surgery or knee replacement surgery.

I will send you a copy of the cover letter.

Kind regards

Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Cato, Marcus
Sent: Thursday, January 13, 2011 3:58 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Importance: High

Hi Andrea

Our reviewer was unable to locate the patient narratives/CRFs based on the pages from the table. As you have submitted many separated PDF files. Could you please include specific names of files and pages for patient narratives, CRFs, and HPAC assessment in the table below.

Warmly,

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, January 13, 2011 12:18 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Dear Marcus,

1) The patient narratives and case report forms (HEAC packets) for the patients reviewed by the hepatic event assessment committee (HEAC) are located in the following sections for each study, please see table below:

2) The HEAC causality assessment summary for each patient can be found listed by the HEAC member name under the HEAC packet.

In general:

Discussion of cases with combined ALT >3x ULN and total bilrubin >2 x ULN with

HEAC causality assessments of majority possible or higher and for other HEAC criteria

cases with majority probable or higher is provided for each individual study in Appendix 1.1 (starting on page 91 of the ISLS) and summarized across the program in Sections 2.4.1 and 2.4.2.

Cases of interest are defined as “at least 2 possible or higher HEAC causality assessments”

Study

Rivaroxaban

Comparator

Total

Source

ROCKET AF 11630

75

76

151

ISLS page 130

All cases located in ROCKET CSR Appendix 4

J-ROCKET 12620

9

5

14

ISLS page 170

All cases located in HEAC packets for J-ROCKET

EINSTEIN 11702 (DVT)

8

12

20

ISLS page 193

All cases located in EINSTEIN DVT CSR/MRR Appendix 16.4.1.3

EINSTEIN Extension (11899)

1

0

1

ISLS page 210

All cases located in EINSTEIN Ext CSR/MRR Appendix 16.4.1.3 and 16.4.1.4

EINSTEIN PE (11702)

(ongoing but open-label)

9

6

15

ISLS page 296

Only 2 cases of interest in ISLS Appendix 7.1.1.5

(other cases not included as this is a ongoing study)

TOTAL

102

99

201

ISLS: pages 64 and 65

ATLAS ACS 2 TIMI 51

Please note that ATLAS ACS 2 TIMI 51 study 13194 is not unblinded and therefore we do not know the number of rivaroxaban and comparator cases. There were a total of 18 subjects with ALT >3xULN and total bilirubin >2xULN concurrently and/or non-concurrently at any time in the study (see Table ISLS1.4 and Table ISLS1.3 in Appendix 7.1.2.1). (page 303 of the ISLS)

The HEAC packets are available in App 7.1.2.5 (four cases of interest)

-

Spontaneous reports

A total of 22 cases of interest were reviewed by HEAC. HEAC packets sent for review and the HEAC reviewer clinical evaluation forms and narratives for cases in Table 8.2.-5 can be found in Appendix 8.2.1.

-

If it would be helpful for us to meet with the Reviewer and walk through the location of any of the data we would be happy to do so.

Let me know if there are any other questions.

Best regards

Andrea

-

-

-

-

-

From: Cato, Marcus
Sent: Tuesday, January 11, 2011 9:00 AM

To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
Importance: High

Hi Andrea,

We need patient narratives and case report forms for all patients (about 200 cases) who were reviewed by hepatic event assessment committee (HEAC). An HEAC causality assessment summary for each patient should also be submitted for review.

Our reviewer was unable to find all the information in the submission. She could only see CRFs for cases (only 20 cases)of the combined ALT>3xULN with total bilirubin >2x ULN cases with at least 2 possible or higher HEAC causality assessments from the Phase 3 clinical program in the submission.

Please submit this information or let us know the location if you have submitted.

Warmly

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, January 06, 2011 12:56 PM
To: Cato, Marcus
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Dear Marcus,

Please note that in the Sponsor Complete response all liver-related safety information is provided in a separate document, the Integrated Summary of Liver Safety (ISLS) which is located in Mod 5.3.5.3.

The *datasets* for the ISLS are provided to FDA in *NDA 202439*, submitted to the Cardio Renal Division yesterday January 5th for the indication of prevention of stroke and non CNS systemic embolism in patients with non-valvular atrial fibrillation.

If you have any questions regarding the ISLS datasets please contact me.

Kind regards

Andrea

From: Kollath, Andrea [PRDUS]
Sent: Monday, January 03, 2011 11:18 AM
To: 'Cato, Marcus'; susan.thompson1@fda.hhs.gov
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response

Dear Dr. Thompson and Marcus,

Happy New Year to both of you.

Attached please find the cover letter of the sponsor complete response submitted Dec 30th last week.

Marcus,

If you have any questions regarding the submission please contact me.

Kind regards

Andrea

Andrea Kollath, DVM,

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

From: Kollath, Andrea [PRDUS]
Sent: Wednesday, December 29, 2010 11:21 AM
To: Cato, Marcus
Subject: NDA 22-406 rivaroxaban Sponsor Complete Response

Dear Marcus,

Happy Holidays to you!

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Sent: Thursday, January 13, 2011 12:18 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Dear Marcus,

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Cases of interest are defined as “at least 2 possible or higher HEAC causality assessments”

Study

Rivaroxaban

Comparator

Total

Source

ROCKET AF 11630

Do you think a response would be possible by 12:00 today?

Thanks

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Tuesday, January 11, 2011 2:03 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Hi Marcus,

There has not been a manufacturing facility change since the action letter.

Regarding the previous question- the case report forms are all in the submission. They are in an appendix for each of the studies discussed. I am going through and making a list as to the locations to try to make it easier. I will send soon.

Kind regards

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Tuesday, January 11, 2011 12:46 PM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
Importance: High

Hi Andrea,

Another question: we need to know if there has been manufacturing facility changes since our action letter. Is this information in the resubmission.

Thanks

~Marcus

From: Cato, Marcus
Sent: Tuesday, January 11, 2011 9:00 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
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Hi Andrea,

We need patient narratives and case report forms for all patients (about 200 cases) who were reviewed by hepatic event assessment committee (HEAC). An HEAC causality assessment summary for each patient should also be submitted for review.

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Please submit this information or let us know the location if you have submitted.

Warmly

~Marcus

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, January 13, 2011 10:22 AM
To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Hi Marcus

I have a question on the list I put together so I will send by noon.

Yesterday we had a “snow” day here so everyone was out. Sorry.

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 13, 2011 8:24 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
Importance: High

Hi Andrea,

Do you think a response would be possible by 12:00 today?

Thanks

~Marcus

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Silver Spring, MD 20903. Thank you.

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To: Cato, Marcus
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Yes. I will send it by 10 AM

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, January 13, 2011 8:24 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response -liver related safety information
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Thanks

~Marcus

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, January 03, 2011 3:58 PM
To: Cato, Marcus
Subject: Updating encryption

Attachments: emfinfo.txt

emfinfo.txt (582 B)

Dear Marcus

I'm checking to see if my new encryption works.

Please let me know if you can read this?

Just hit reply and send back please.

Thanks

Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Monday, January 03, 2011 11:18 AM
To: Cato, Marcus; Thompson, Susan (CDER)
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406 rivaroxaban Sponsor Complete Response

Attachments: NDA 22-406 Dec 27 2010 CR Cover letter to FDA .pdf

NDA 22-406 Dec 27 2010 CR Cove...

Dear Dr. Thompson and Marcus,

Happy New Year to both of you.

Attached please find the cover letter of the sponsor complete response submitted Dec 30th last week.

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phone 908-927-6522 ; cell 215-262-4126

From: Kollath, Andrea [PRDUS]
Sent: Wednesday, December 29, 2010 11:21 AM
To: Cato, Marcus

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Tuesday, November 09, 2010 11:30 AM
To: Cato, Marcus
Subject: RE: NDA 22-406 Rivaroxaban - CR - Foreign Labeling Question

Attachments: emfalert.txt

emfalert.txt (1 KB)

Thank you.

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Tuesday, November 09, 2010 10:48 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 Rivaroxaban - CR - Foreign Labeling Question

Hi Andrea,

Your proposal is acceptable.

Thanks

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Monday, November 08, 2010 2:51 PM

To: Cato, Marcus
Subject: RE: NDA 22-406 Rivaroxaban - CR - Foreign Labeling Question

Hi Marcus

Can you let me know if this is an acceptable proposal?

Thanks

Andrea

From: Kollath, Andrea [PRDUS]
Sent: Wednesday, October 27, 2010 1:34 PM
To: Cato, Marcus
Subject: NDA 22-406 Rivaroxaban - CR - Foreign Labeling Question

Dear Marcus,

We are preparing our Complete Response to FDA CR Letter of May 27, 2009.

Under Safety Update, Question 8, we are asked to provide English translations of current approved foreign labeling not previously submitted.

The current list of international approvals for rivaroxaban is over 100 countries. Please see attached list.

We propose to provide English translations for the following countries which we think provide a representative example for the major geographic regions and major markets.

1. European Union
2. Switzerland (non-EU country in Europe)
3. Russia
4. Canada
5. Mexico
6. Brazil
7. Australia

8. New Zealand

9. China

10. India

11. Kenya

12. U.A.E.

13. South Africa

Is this acceptable to the Division of Hematology Products?

Best regards,

Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

920 Route 202, PO Box 300

Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

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12. U.A.E.
13. South Africa

Is this acceptable to the Division of Hematology Products?

Best regards,

Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

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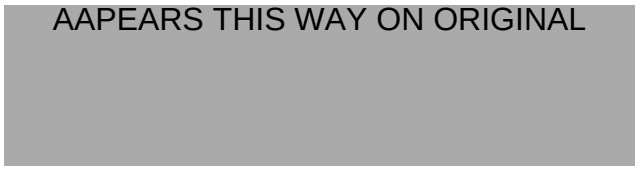
Raritan NJ 08869

phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com


AAPEARS THIS WAY ON ORIGINAL

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Wednesday, October 27, 2010 1:34 PM
To: Cato, Marcus
Subject: NDA 22-406 Rivaroxaban - CR - Foreign Labeling Question

Attachments: Xarelto (rivaroxaban) regulatory approval status _16062010.pdf; emfalert.txt


Xarelto varoxaban) regulat


emfalert.txt (1 KB)

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akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Friday, October 15, 2010 10:30 AM
To: Cato, Marcus
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Attachments: emfalert.txt

emfalert.txt (1 KB)

Thank you.

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Friday, October 15, 2010 9:42 AM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Hi Andrea

It is acceptable to link to the information, no need to submit twice. We have been discouraging submission of duplicate information.

Thanks

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, October 14, 2010 3:29 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Hi Marcus,

I just want to make sure it is acceptable to FDA? We do not wanted to get cited for missing information.

Thanks

Andrea

From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, October 14, 2010 3:22 PM
To: Kollath, Andrea [PRDUS]
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Hi Andrea,

I am not sure the exact details but if its been submitted to the gateway previously... you should be able to link to it in your response... do you have a target date for your response?

Thanks

~Marcus

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Thursday, October 14, 2010 3:13 PM
To: Cato, Marcus
Subject: NDA 22-406 CR- Question on re-submission of documents

Hi Marcus,

We have a question on how to handle the documents that were already submitted to the NDA such as the Bayer and (b) (4) audits that DSI is currently reviewing.

Do we resubmit those documents again in the CR or should we simply refer to them or can we link to them?

This will help with our planning.

Thank you and Best regards,

Andrea

Andrea Kollath, DVM,
Global Regulatory Affairs

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akollath@its.jnj.com

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, October 14, 2010 3:26 PM
To: Cato, Marcus
Subject: RE: NDA 22-406 CR- Question on re-submission of documents

Attachments: emfalert.txt

emfalert.txt (1 KB)

Hi Marcus,

We plan to submit towards the end of December this year.

Andrea

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phone 908-927-6522 ; cell 215-262-4126

akollath@its.jnj.com

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARCUS A CATO
06/07/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-406

MEETING MINUTES

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 13, 2009. The purpose of the meeting was to discuss the potential planned unblinding of data related to your application.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type C
Meeting Category:	Clinical, Guidance
Meeting Date and Time:	November 13, 2009, 10:00 AM - 11:00 AM EST
Meeting Location:	CDER WO Building 22, conference room 1419
Application Number:	NDA 22-406
Product Name:	Xarelto™ (Rivaroxaban) Tablets
Indication:	Prophylaxis of Deep Vein Thrombosis (DVT)/Pulmonary Embolism (PE) in hip or knee surgery
Sponsor/Applicant Name:	Johnson & Johnson Pharmaceutical Research and Development (J&J)
Meeting Chair:	Dr. Dwaine Rieves
Meeting Recorder:	Mr. Marcus Cato

FDA ATTENDEES

OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., M.P.H., Clinical Reviewer
Diane Leaman, Safety Regulatory Project Manager
Ira Krefting, M.D., Safety Deputy Director

OFFICE OF DRUG EVALUATION I/DIVISION OF CARDIOVASCULAR & RENAL PRODUCTS

Stephen Grant, M.D., Deputy Director
Robert Temple, M.D., Director Office of Drug Evaluation I/Office of Medical Policy

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer
Gwen Zornberg, M.D., Medical Team Leader
Mark Avigan, M.D., Office Associate Director

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

John R. Senior, M.D., Medical Officer (Hepatotoxicity)
Carr, Catherine, M.S., Regulatory Health Project Manager

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader
Robert ONeill, Ph.D., Office Director

OFFICE OF TRANSLATIONAL SCIENCES

Marc Walton, M.D., Associate Director

SPONSOR ATTENDEES

J&J

Peter DiBattiste, M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters , MD Franchise Medical Leader
Lloyd Haskell , MD, Compound Development Team leader
Leonard Oppenheimer, PhD. Statistical Sciences
John Zhang PhD. Statistical Sciences
Harry Flanagan, DO, Post-Marketing Benefit Risk Management
G.K. (Dina) Anand MD, Post-Marketing Safety Franchise Leader
Sigmond Johnson, MS, MBA Program Coordination
Andrea Masciale, Regulatory Affairs, FDA Liaison Office
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Kollath, DVM, Regulatory Affairs

Bayer

Scott D. Berkowitz, MD, VP, Global Clinical Dev. Head, Thrombosis and Hemostasis
Aasia Bhatti, MD, Deputy Director, Global Pharmacovigilance
Andrea Nadel PhD, Statistical Sciences
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology
Harald Kallabis, Ph.D., Global Project Leader

1.0 BACKGROUND

In a letter dated May 29, 2009, J&J requested a meeting to obtain clarification on specific items detailed in the May 27, 2009, FDA Complete Response Letter (CR). On June 19, 2009, FDA and J&J met to discuss the CR.

In a letter dated July 2, 2009, J&J submitted a proposed liver adjudication panel (LAP) procedural charter, as follow-up to the Type A meeting held on June 19, 2009. On July 31, 2009, FDA met with J&J, to discuss their proposed LAP charter. At the meeting, FDA agreed to meet with J&J again, to discuss the possible unblinding of potential *Hy's Law* cases and other safety conveyance topics, after further internal discussions could be held.

MEETING OBJECTIVES:

To discuss the potential planned unblinding of data related to the application.

2. DISCUSSION

FDA recommends that J&J submit the LAP output to the NDA in a complete response to the Agency action letter. All of the data in the submission should be unblinded (including treatment assignment codes). Alternatively, the sponsor could submit a letter to the application authorizing an unblinded statistician to submit the information to the NDA.

J&J noted that three new reviewers have been selected for the liver adjudication panel and that adjudication will not be by consensus process but rather each adjudicator will adjudicate each case independently. Using a cut-off date of September 15, 2009, it has identified 72 potential *Hy's Law* cases. J&J anticipates submitting the following:

- The fully blinded data package reviewed by the LAP
- The evaluation forms from the LAP review
- Summary Tables

J&J is planning to submit all information blinded. FDA informed J&J that this plan is not acceptable. FDA inquired about J&J's reluctance to unblind the data.

J&J stated that it does not want to jeopardize the four large ongoing trials. It is concerned that unblinding may introduce operational bias and it would like to unblind as few cases and people (including as few FDA reviewers) as possible. Approximately 10 of the 72 subjects are still on study drug as they have not met the discontinuation criteria. FDA clarified that it has to know the safety data and outcomes for these patients and it has to look at the data to make a determination: FDA will be reviewing the data and performing its own analyses. J&J responded that its proposed plan was to submit the full LAP data package along with adjudications from the panel and to have FDA identify cases of interest it would like to discuss at a meeting with the cross study Data and Safety Monitoring Board (DSMB). FDA stated that meeting with J&J's DSMB would not be helpful, since the unblinded safety data for the potential Hy's law cases

need to be submitted to the NDA. FDA will be reviewing the data and doing its own analyses independently.

J&J stated that very few of its potential *Hy's Law* cases have been unblinded because they have not meet the per protocol criteria to be unblinded. J&J is very concerned about introducing operational bias and this concern is based on previous interactions with FDA.

FDA is concerned that the Rivaroxaban NDA has an incompletely developed safety database. FDA is concerned that there are 72 potential *Hy's Law* cases and can not approve the pending NDA without full access to the safety data.

FDA clarified that the proposal to limit the number of FDA reviewers who have access to unblinded data is not acceptable. FDA reminded J&J that an alternative to submitting the unblinded data is to wait until the ongoing studies have been completed before responding to the Agency action letter. However, FDA is not encouraging J&J to delay responding. FDA acknowledges that generally sponsors are encouraged to unblind as few subjects in ongoing trials as possible. FDA stated that the situation is unusual in that FDA needs to review safety data from ongoing trials in order to evaluate the safety of rivaroxaban as part of a NDA for another indication.

FDA acknowledges that, in general, it does not anticipate that all 72 cases will actually be *Hy's Law* cases; however, it does need to be able to unblind data for identified cases of interest. J&J wanted assurance that unblinding the data would not negatively impact the FDA perception of the integrity of the ongoing trials. FDA responded that the proposed limited unblinding should not result in a judgment that the integrity of the studies had been compromised, provided the process was pre-specified and carried out according to plan. J&J responded that, if the unblinding of this data will not compromise the studies; it would submit the data itself rather than have an unblinded statistician submit the information on its behalf.

FDA requested that J&J submit the following data in its complete response where ALT, TB and ULN refer to alanine aminotransferase, total bilirubin and upper limit of normal, respectively:

A. Combined ALT >3xULN and TB >2xULN case information with treatment codes blinded (i.e., the clinical information pertaining to those patients the company has previously identified as potential *Hy's Law* cases based upon plans submitted to the FDA)

B. Tabular distribution of ALT >3x ULN , ALT > 5X, ALT > 10X data presented by study, by threshold and by treatment group- (A vs. B)

C. Tabular distribution of concurrent ALT > 3X x ULN and TBL > 2x ULN (within one month) presented by study and by treatment group (A vs. B)

D. FDA would review the combined ALT + TB cases (potential *Hy's Law* cases) and request treatment codes for specific cases. It would also request unblinded tabular data (i.e., A and B group identified as to specific treatment assignment) if needed during its review of the liver data.

J&J agreed to A. through D. (above).

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
J&J to submit safety data in its Complete Response as specified above	Sponsor	N/A

5.0 ATTACHMENTS AND HANDOUTS

None.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22406	ORIG-1	JOHNSON AND JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT LLC	XARELTO (RIVAROXABAN) ORAL 10 MG

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/s/

MARCUS A CATO
12/10/2009

RAFEL D RIEVES
12/10/2009

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on July 31, 2009. The purpose of the meeting was to discuss your proposed liver adjudication panel procedural charter submitted as follow-up to the Type A meeting with the Agency on June 19, 2009; held to obtain clarification the May 27, 2009, FDA Complete Response Letter.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: July 31, 2009
TIME: 10:00 AM - 11:00 AM EST
LOCATION: CDER WO 2201 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson & Johnson Pharmaceutical Research and Development (J&J)
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., M.P.H., Clinical Reviewer

OFFICE OF NEW DRUGS/ OFFICE OF DRUG EVALUATION I/DIVISION OF
CARDIOVASCULAR & RENAL PRODUCTS

Stephen M. Grant, M.D., Clinical Team Leader

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

John R. Senior, M.D., Medical Officer (Hepatotoxicity)

EXTERNAL ATTENDEES:

J&J

Martin Fitchet, MD, Global TA Head, CV & Metabolism
Gary Peters , MD Franchise Medical Leader

Lloyd Haskell , MD, Compound Development Team leader
Mehul Desai MD, Clinical
Debra Karvois, Clinical Project Scientist
Leonard Oppenheimer, PhD. Statistical Sciences
John Zhang PhD. Statistical Sciences
Harry Flanagan, DO, Post-Marketing Safety Expert, Benefit Risk Management
G.K. (Dina) Anand MD, Post-Marketing Safety Franchise Leader
Sigmond Johnson, MS, MBA Program Coordination
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Masciale, Regulatory Affairs, FDA Liaison Office
Andrea Kollath, DVM, Regulatory Affairs

BAYER

Scott D. Berkowitz, MD, FACP, FACC, VP, Head, Thrombosis, Hemostasis, CV and Coagulation
Sabine Dittmar MD, Global Pharmacovigilance
Andrea Derix, PhD, Sen. Global Regulatory Strategist
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology
Alice Benson PhD, Principal Statistician, Global Clinical Statistics,
Martin Homering PhD, Statistical Sciences

BACKGROUND:

In a letter dated May 29, 2009, J&J requested a meeting to obtain clarification on specific items detailed in the May 27, 2009, FDA Complete Response Letter (CR). On June 19, 2009, FDA and J&J meet.

In a letter dated July 2, 2009, J&J submitted a proposed liver adjudication panel procedural charter, as follow-up to the Type A meeting with the Agency on June 19, 2009. On July 29, 2009, FDA sent J&J, via e-mail, draft responses to the questions raised in the June 2, 2009, submission (See FDA preliminary comments below).

MEETING OBJECTIVES:

To discuss the J&J proposed liver adjudication panel procedural charter, submitted as follow-up to the Type A meeting with the Agency on June 19, 2009.

DISCUSSION POINTS:

J&J clarified that (b) (6) was not a part of the original liver adjudication panel (LAP). He performed a separate adjudication and presented these findings at the March 19, 2009, advisory committee meeting (AC). J&J did not intend to include (b) (6) in the new liver adjudication panel but intended to use him as a consultant.

FDA commented that its objection is to (b) (6) participating in the adjudication process and not to him participating as a consultant or reviewing the LAP output. With regard to other members from the previous LAP, FDA emphasized that its concern is objectivity; previous members have publicly expressed an opinion on the existence of liver toxicity. The FDA objection is not based on the qualifications of the panel members but is to ensure objectivity.

FDA reminded J&J that it has outlined what it believes to be the most persuasive proposal in previous communications. J&J stated that its current proposal is to send the data to three different reviewers to perform an independent five-scale assessment. The reviewers would independently examine and record their opinion and then meet to build consensus.

FDA emphasized that it would like a clear, independent, output, without the reviewers discussing amongst themselves. J&J proposed collapsing the design to a locked *yes/no* output for each reviewer (as to whether the enzyme elevations appear drug related) prior to collecting the five-scale assessment. FDA stated it is important to preserve the original output/opinions of the LAP reviewers, to lock a *yes/no* vote and to ensure that FDA have available all data that the LAP relievers had. FDA emphasized that it needs a *forced-opinion* for each case.

J&J inquired about what studies to include. FDA stressed that all potential *Hy's Law cases* from all studies, up to the safety update, be included.

FDA expressed concern about patients who dropped out of the study and were not followed by the central and local laboratories. FDA requested that J&J identify and follow-up with the central and local laboratories for all patients that dropped who were not per-protocol (some patients had an alanine aminotransferase (ALT) reach three times the upper limit of normal (ULN) but dropped-out from the trial). FDA requested full accounting and an active query for patients that discontinued. J&J agreed to query these patients and provide summary tables, though they will not be adjudicated.

J&J requested FDA concurrence with the proposal to adjudicate only the ongoing studies, and to not re-adjudicate RECORD potential *Hy's Law cases*. FDA concurred.

J&J stated it intended to submit all information on potential *Hy's Law cases* and the same blinded data reviewed by the LAP as part of the complete response to the FDA action letter.

FDA stated it envisions a process in which it would receive:

- The original LAP adjudication output
- A complete LAP adjudication summary report
- The full blinded data package reviewed by the LAP

FDA would review the LAP output and re-adjudicate cases-of-interest as needed. FDA expects that the DSMB would produce a report; however, there would be no joint overview (FDA & DSMB) of the adjudication output.

FDA noted that the process for conveying the liver safety data to the agency remains under discussion and under one scenario, FDA envisions receiving only blinded data for potential *Hy's Law cases* while the adjudication output would also go to the DSMB. FDA would meet with the DSMB to discuss the results (in a controlled environment) and FDA will not archive unblinded data to the application. FDA will archive the conclusion of whether drug-induced liver injury is present or not.

FDA emphasized that it may only need to archive the DSMB decision.

The sponsor agreed with the FDA outline and considerations.

FDA and J&J discussed the number of potential *Hy's Law cases* to be adjudicated (approximately 50-60). FDA commented that with so few cases J&J may wish to consider unblinding all the potential *Hy's Law cases*, particularly if these cases would be unblinded anyway. J&J expressed concern about unblinding these cases. FDA agreed to meet with J&J again, to discuss potential unblinding, after further internal discussion. No conclusion was reached regarding the unblinding/process for conveying safety data from the ongoing studies to the NDA.

DECISIONS (AGREEMENTS) REACHED:

- J&J proposed collapsing the design to a locked "yes/no" output for each reviewer prior to collecting the five-scale assessment. FDA emphasized that it needs a *forced-opinion* for each case.
- FDA stressed that all potential *Hy's Law cases* from all studies, up to the safety update, be included in the LAP adjudication. J&J agreed
- J&J to adjudicate only the ongoing studies, and not re-adjudicate RECORD cases.
- J&J agreed to submit all information on potential *Hy's Law cases* and the same blinded data reviewed by the LAP as part of the complete response to the FDA action letter.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- FDA agreed to meet with J&J again, to discuss potential unblinding of potential *Hy's Law cases* and other safety conveyance topics, after further internal discussion.

ACTION ITEMS:

- FDA to meet with J&J after internal discussion.

ATTACHMENTS/HANDOUTS:

- FDA preliminary comments

Introductory Comment: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **July 31, 2009** between **Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&J)** and the FDA. This material is shared to promote a collaborative and successful discussion at the meeting; the minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, to the purpose of the meeting or to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.

Draft Preliminary Comments for J&J July 31 teleconference regarding Liver Adjudication Panel

1. The documentation of Liver Advisory Panel (LAP) procedures appears much more developed, compared to those used in the prior adjudication process.

2. Several of our prior recommendations were not incorporated into the LAP procedures. We continue to believe that incorporation of our prior recommendations is more likely to provide a definitive outcome and encourage you to reconsider our prior major recommendations. In particular we reiterate that the new adjudication should be conducted solely by individuals who were not involved in the previous liver adjudication panel. Most notably, we are very concerned that the inclusion (b) (6) within the new adjudication process is inappropriate, based upon his conclusions voiced at the Advisory Committee. At a minimum, we encourage you to exclude (b) (6) from the adjudication/review process.

3. We have the following specific comments:

a. We do not concur with the plan for documentation of individual clinical adjudicator conclusions, followed by the formation of a consensus conclusion for each patient. We continue to believe that adjudication should be conducted independently by two individuals with adjudication by a third if there is disagreement.

b. We recommend you modify section 4 of the LAP procedural document to also state that applicable "cases" from the post-marketing experience will be adjudicated. We recognize that available data may be more limited for these "cases" but inclusion of these cases within the final report will help verify that all available data have been analyzed for signals of severe liver injury.

c. We acknowledge that you plan to modify the LAP procedural document to expand the case selection criteria to include cases that occur within 4 weeks "after the ALT elevation."

d. We are particularly unclear about the process outlined on pages 9 and 10 of your cover letter. For example, we do not understand the point of inclusion of FDA participants in a blinded review of index cases (item 1). Additionally, we are unclear of the individuals representing "the designated clinical reviewers" (item 5). We request revision of these procedures following our discussion. In general, we expect:

i. Within your complete response, submission of copies of all source information and case report forms used in the adjudication process. Submission of this information will allow FDA to perform a detailed review/readjudication of any cases that appear of particular concern, based upon a preliminary review of the information.

ii. Development of procedures in which FDA representatives will meet with members of the Data Safety and Monitoring Board in order to have the members convey their unblinded review findings, conclusions and the basis for their conclusions.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22406	ORIG-1	JOHNSON AND JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT LLC	XARELTO (RIVAROXABAN) ORAL 10 MG

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/s/

MARCUS A CATO
10/13/2009

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 22-406

GENERAL ADVICE

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Dr. Kollath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to your July 8, 2009 submission, containing your proposed supplemental audit plan.

We have reviewed the referenced material and have the following comments and recommendations:

1. We agree with the number of sites selected and the number of subjects to be audited at each site.

2. We agree that you will submit individual site reports as well as a separate summary report as outlined in the proposal.

3. The Data Verification Tool appears acceptable to capture all necessary information.

4. The summary report should include the exact role of the Bayer representative in the audit.

5. We request that you submit an updated timeline for the supplemental audit completion.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, MD
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

RAFEL D RIEVES
08/14/2009

RECORD OF TELEPHONE CONVERSATION

NDA: 22-406

Product: Rivaroxaban

Today's date: August 10, 2009

Speakers:

For FDA: Dwaine Rieves and Marcus Cato
For Johnson and Johnson: Gary Peters and Peter Debateste

FDA called the company today to request perspectives regarding the following items:

1. How many patients do they anticipate will need adjudication and of these, how many have already been unblinded to treatment assignment?

Response: The company plans adjudication of patients from five on-going clinical studies:

-Magellan
-Rocket
-Rocket/Japan
-Einstein
-Atlas AC

The company noted that enrollment in Atlas AC is early/enrollment in other studies in near completion/or completed. The company "roughly" estimates about 60 patients will need adjudication. Of these, the company estimates that no more than 10% (6 patients) will have been unblinded since the protocols generally did not anticipate unblinding.

2. Could the company restate its position regarding unblinding of all index cases for adjudication? FDA notes that, since these patients will have stopped drug and the sample sizes in the studies are so very large, it seems reasonable to unblind all patients who are to undergo adjudication.

Response: The company stated they remain strongly opposed to unblinding of the index cases because:

a. Unblinding presents logistical challenges/need for protocol amendments or cleared "exceptions" to satisfy European and US expectations since the unblinding had not been a component of the protocol plans.

b. Concern that ad hoc unblinding might reveal findings that necessitate protocol modifications, particularly for Atlas AC and performance of this form of safety

monitoring outside of the DSMB/protocol plans may ultimately raise questions of study conduct.

The company also emphasized that the assessment of important liver signals relies not only on the adjudication results for index patients but also upon the active/control comparisons of the distribution of patients with excessive aminotransferase elevations (as they had outlined in their plans). For this reason, they had proposed that the "cross study DSMB" have the main responsibility for examining unblinded adjudicated case distributions as well as tabular summaries of the distribution of patients with excessive aminotransferase levels. The company noted that the DSMB charter allows "consultants" to be added to the DSMB review proceedings and, in this context, the DSMB may choose to allow a small number of FDA staff to join the meeting to review the unblinded data (if necessary).

FDA closed the conversation by stating that discussions are on-going within the agency regarding the plans and follow-up from these discussions will be provided to the company.

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/s/

RAFEL D RIEVES
08/13/2009

Memorandum

To: NDA 22-406

CC: Eldon Leutzinger, Josephine Jee, Rik Lostritto, Ph.D.

From: Sarah C. Pope, Ph.D.

Date: 5/27/2009

Re: Final CMC recommendation for NDA 22-406

NDA 22-406 was initially submitted on 28-JUL-2008 and was granted a standard review by the Agency. Chemistry Review #1 (dated 29-MAR-2009) identified several Chemistry, Manufacturing and Controls (CMC) deficiencies which should be conveyed in the action letter.

Resolution of these CMC deficiencies is necessary prior to a CMC recommendation for approval of NDA 22-406. Additionally, at the time of finalization of the 29-MAR-2009 CMC review, an overall recommendation from the Office of Compliance had not been received.

This memo serves to update that determination. The Office of Compliance issued an overall acceptable recommendation for this application on 26-MAY-2009. However, from a CMC perspective, approval of NDA 22-406 cannot be recommended until the outstanding CMC deficiencies are adequately resolved.

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/s/

Sarah Pope
5/27/2009 12:15:48 PM
CHEMIST

Richard Lostritto
5/27/2009 12:24:31 PM
CHEMIST

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE:	May 12, 2009
TIME:	12:30 – 13:00 ET
LOCATION:	White Oak Conference Room 2560
APPLICATION:	NDA 22-406
SPONSOR:	Johnson & Johnson Pharmaceutical Research and Development (J&J)
DRUG NAME:	Xarelto (Rivaroxaban) tablets
TYPE OF MEETING:	Teleconference
MEETING CHAIR:	Sarah Pope, Ph.D.
MEETING RECORDER:	Don Henry

FDA PARTICIPANTS:

Sarah Pope, PhD., Branch Chief
Eldon Leutzinger, Ph.D., Pharmaceutical Team Leader
Josephine Jee, Ph.D., Chemist
Marcus Cato, Regulatory Project Manager
Don Henry, Regulatory Project Manager

EXTERNAL PARTICIPANTS:

Bayer attendees
Robert Kelly, Director CMC and Marketed Products, Bayer HealthCare
Deborah Flint, Associate Director CMC, Bayer HealthCare
Larry Winick, MA. Global Regulatory Strategist; Hematology/Cardiology

J&J attendees
Nancy Micalizzi, Associate Director, CMC Regulatory
Donald Doyle, MS, Director, ChemPharm Leader
Frank J DeLuccia, Ph.D. , Vice President, Global CMC Regulatory Affairs
Sanjay Jalota, MRPharmS, Senior Director, Global Regulatory lead
Andrea Kollath, DVM, Director, Regulatory Affairs

BACKGROUND:

The FDA filed deficiency notifications for Drug Master Files 21580, 21581, and 21592 in support of this application (NDA 22-406) for Xarelto (Rivaroxaban) tablets. Based on the letters, J&J requested a teleconference meeting to discuss the following deficiency:

- Based on the 9 months of long-term stability data at 25°C/60% RH and 6 months at 30°C/75% RH submitted of rivaroxaban tablets in HDPE bottles and (b) (4) blisters, a (b) (4) expiration dating period is the maximum that can be granted at this time.

J&J provided the following background information for the meeting:

J&J respectfully notes that the (b) (4) expiry is not acceptable for the Gurabo finished product. Please reconsider the expiry based on the following:

1. The primary stability data for the tablets was generated on batches manufactured at Bayer's Leverkusen site as described in 3.2.P.8 of J&J PRD DMF 21592. Manufacturing site equivalence was established based on a comparison of tablet manufacturing processes, batch release data and stability data. This was agreed with the Agency during the Pre-NDA Meeting correspondence. (Agency responses dated Nov 7, 2008 to our briefing document questions).
2. Also, it is our understanding based on the pre-NDA meeting (FDA response to question 3 in the briefing document) that the expiry would be granted based on a combination of the primary stability data, the Bayer supportive data, as well as the site data. The Bayer DMF supportive data also included (b) (4) open container data. The J&J Gurabo site stability data confirms the stability profile of the product. It should not be the sole dataset to base expiry on.
3. The February 23, 2009 amendment to J&J DMF 21592 contained a 9-mos stability update on the Gurabo site stability batches. We currently also have 12-month stability data and the statistical analysis for both the 9 month and the 12 month data, which could be provided. However, we would like to know if this would be considered a major amendment, necessitating additional review time.

THE TELECONFERENCE DISCUSSION

1. FDA indicated that upon review of the information presented above, an expiry of (b) (4) would be granted for the bottle configurations. Only (b) (4) expiry could be granted for the blisters since they represented worst case and there was only 9-months real-time data for the commercial configurations. However, J&J indicated that the cross-referenced DMF 21580 provides a statistical evaluation of the data that would support a (b) (4) expiry. FDA asked J&J to confirm the location of the statistical analysis and agreed to re-evaluate that data in relationship to the expiration dating period for the blister configuration.

2. Additional Meeting Discussion: J&J indicated that during a previous teleconference with the Division of Medical Imaging and Hematology, they were informed that there were major CMC issues with the applications. J&J asked whether there were issues, in addition to the deficiencies identified in the DMF. FDA expressed that the CMC review is still ongoing and that J&J will be notified of any issues in a timely manner.

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/s/

Don Henry
5/14/2009 09:28:59 AM
PROJECT MANAGER FOR QUALITY

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE:	May 12, 2009
APPLICATION NUMBER:	NDA 22-406

BETWEEN:

Name:	Sanjay Jalota, MRPharmS Regulatory Global Regulatory Lead
	Andrea F. Kollath, DVM Director, Regulatory Affairs
e-mail:	AKollath@its.jnj.com SJalota@its.jnj.com
Representing:	Johnson and Johnson Pharmaceutical Research and Development

AND

Name:	Marcus Cato, M.B.A., Regulatory Project Manager Division of Medical Imaging and Hematology Products HFD-160
SUBJECT:	Final study report for ATLAS ACS TIMI 46

Cato, Marcus

From: Cato, Marcus
Sent: Tuesday, May 12, 2009 4:44 PM
To: 'Jalota, Sanjay [PRDUS]'
Cc: Kollath, Andrea [PRDUS]
Subject: RE: ATLAS ACS TIMI 46 - RE: Questions on NDA 22-406

Dear Sanjay,

My apologies for my delayed response. The reviewers regard the ATLAS study as important. It is at your discretion whether or not to submit it to the NDA at the present time. As discussed in the telephone conversation of May 11 between FDA and Dr. Kronig, the review team is finalizing all reviews at the present time and the division plans to close out this review cycle shortly. Hence, the division does not envision reviewing the ATLAS study during this review cycle. In general, we suggest you await the results of this review cycle prior to submitting additional data (including the ATLAS study).

Thanks

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

From: Jalota, Sanjay [PRDUS] [mailto:SJalota@its.jnj.com]
Sent: Thursday, May 07, 2009 3:51 PM
To: Cato, Marcus; Kollath, Andrea [PRDUS]
Subject: ATLAS ACS TIMI 46 - RE: Questions on NDA 22-406

Hi Marcus,

Hope all is well. We submitted the ATLAS ACS TIMI 46 to IND 75,931. Attached is the cover letter
As per the March 20, 2009 AdCom discussions where DMIHP mentioned they had not seen the final study report, please let me know if we need to formally submit the cover letter or the report (~15,000 pages) to the NDA

Thanks and best regards
Sanjay

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/s/

Marcus Cato

5/14/2009 08:03:24 AM

CSO

RECORD OF TELEPHONE CONVERSATION

NDA 22-406 (Rivaroxaban)

Today's date: May 11, 2009

Speakers: Marcus Cato and Dwaine Rieves for FDA
Michael Kronig for Johnson and Johnson

FDA returned a phone call to Dr. Kronig (908-727-2526) after Dr. Kronig had left a voice mail on Dwaine Rieves' line. FDA made the following points:

-the NDA is in the "wind down" phase and all primary reviews should have been completed by now

-FDA anticipates completing this review cycle with an action

-FDA anticipates the need for resolution of CMC issues, certain clinical data integrity issues as well as the need for additional clinical data that will help evaluate the risk (if any) for severe liver toxicity

Dr. Kronig acknowledged that they were hoping for a first cycle approval or a major amendment approach but they would deal with other responses.

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/s/

Rafel Rieves
5/11/2009 05:38:16 PM
MEDICAL OFFICER

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	May 1, 2009
TIME:	1:00 PM - 3:00 PM EST
LOCATION:	White Oak CSU Building Room 2047
APPLICATION:	NDA 22-406
SPONSOR:	Johnson and Johnson Pharmaceutical Research and Development (J&J)
DRUG NAME:	Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING:	Regulatory Briefing
MEETING CHAIR:	Dr. John Jenkins
MEETING RECORDER:	Mr. Marcus Cato, Ms. Diane Leaman

FDA ATTENDEES:

REGULATORY BRIEFING PANEL

John K Jenkins, M.D., Director, Office of New Drugs
Richard Pazdur, M.D., Director, Office of Oncology Drug Products
Robert Temple, M.D., Director, Office of Medical Policy
Janet Woodcock M.D., Director, Office of the Center
Douglas Throckmorton, M.D., Deputy Director, Center for Drug Evaluation and Research
Gerald Dal Pan, M.D., Director, Office of Surveillance and Epidemiology
Robert ONeill, Ph.D., Director, Office of Biostatistics
Rosemary Roberts, M.D., Director, Office of Counter-Terrorism and Emergency Coordination
Solomon Sobel, M.D., Associate Director, Science and Research Staff
David Jacobson-Kram, M.D., Associate Director, Office of New Drugs

FDA PRESENTERS

Kathy Robie Suh, M.D., Ph.D., Team Leader, Division of Medical Imaging and Hematology Products
Min Lu, M.D., M.P.H., Medical Officer, Division of Medical Imaging and Hematology Products
Jyoti Zalkikar, Ph.D., Team Leader, Division of Biometrics V
Qing Xu, Ph.D., Reviewer, Division of Biometrics V
Joseph Grillo, Pharm.D., Reviewer, Division of Clinical Pharmacology V
Kate Gelperin, M.D., M.P.H., Medical Officer, Division of Epidemiology I

FDA ATTENDEES

Ian Waxman, Ph.D., Division of Clinical Evaluation & Pharmacology/Toxicology
Keith Burkhart, M.D., Office of New Drugs
Wiley Chambers, M.D., Division of Anti-Infective and Ophthalmology
Jennifer Harris, M.D., Division of Anti-Infective and Ophthalmology
Joseph Stalder, Division of Special Pathogen and Transplant Products
Jane Liedtka, M.D., Division of Dermatology and Dental Products
Melinda McCord, Ph.D., Division of Dermatology and Dental Products
Michael Monteleone, M.D., Division of Cardiovascular and Renal Products
Robert Fiorentino, M.D., Division of Cardiovascular and Renal Products
Steven Grant, M.D., Division of Cardiovascular and Renal Products
Ann Farrell, M.D., Division of Drug Oncology Products
Ke Liu, M.D., Division of Drug Oncology Products
Robert Justice, M.D., Division of Drug Oncology Products
Mohab Alexander, M.D., Division of Medical Imaging and Hematology Products
Diane Leaman, Division of Medical Imaging and Hematology Products
Ira Krefting, M.D., Division of Medical Imaging and Hematology Products
Marcus Cato, M.B.A., Division of Medical Imaging and Hematology Products
Timothy Lape, Pharm.D., Office of Surveillance and Epidemiology
Tselaine Jones-Smith, Pharm.D., Division of Medical Error and Preventions Analysis
Kathryn O'Connell, M.D., Division of Risk Management
Phuong Nina Ton, Pharm.D., Review Management Staff
Lisa Kubaska, Division of Drug Information
Ram Tiwari, Ph.D., Office of Biostatistics
Kate Dwyer, Ph.D., Division of Biometrics III
Rima Izem, Ph.D., Division of Biometrics IV
Aloka Chakravarty, Ph.D., Division of Biometrics V
Chava Zibman, Ph.D., Division of Biometrics I
Min Min, Ph.D., Division of Biometrics I
Li Zhang, Ph.D., Office Of Clinical Pharmacology
Lanyan Fang, Ph.D., Division of Clinical Pharmacology III
John Lazor, Ph.D., Division of Clinical Pharmacology IV
Nam Atiqur Rahman, Ph.D., Division of Clinical Pharmacology V
Young Moon Choi, Ph.D., Division of Clinical Pharmacology V

EXTERNAL ATTENDEES:

None

BACKGROUND:

NDA 22-406 is an application for Xarelto (rivaroxaban), an anticoagulant, for short-term use in prophylaxis of venous thromboembolism (VTE) in patients undergoing elective hip replacement surgery and in patients undergoing elective knee replacement surgery. On March 19, 2009, FDA held an Advisory Committee (AC) meeting regarding the clinical data in NDA 22-406, where the FDA emphasized that, in regard to efficacy, data from four clinical studies demonstrated statistically significant outcomes, predominantly due to asymptomatic venographic findings. The AC discussion focused upon safety considerations such as bleeding, the potential for liver toxicity, and considerations of whether or not the long-term data were essential for the initial short-term risk-benefit assessment. Suggestions of liver toxicity were evident in the short-term studies. To address this concern for a liver toxicity signal, the sponsor presented summary liver test data from a recently completed study (the ATLAS ACS TIMI 46 Clinical Study) in which subjects received six months of rivaroxaban therapy. The final study report and details of this study have not been made available for FDA review. Ultimately, the Advisory Committee provided a favorable recommendation for the risk-benefit assessment based upon considerations of the available clinical data.

MEETING OBJECTIVES:

To discuss the division's plan to issue a Complete Response letter.

DISCUSSION POINTS:

The Division presented slides (see attached).

Prior to the statistical presentation, the Division noted that the primary endpoint of the study [a composite of any deep vein thrombosis (DVT) (venographically demonstrated, symptomatic or non-symptomatic), non-fatal pulmonary embolism (PE), and death from any cause] supported the efficacy of the drug. The statistical presentation would focus on the exploratory pooled analyses of "symptomatic venous thromboembolism (VTE)."

The panel commented that the exploratory analysis of evidence of superiority of rivaroxaban compared to enoxaparin does not meet the regulatory standard for superiority. Proximal VTE is a more clinically meaningful outcome than asymptomatic distal VTE; VTE location should be considered when assessing the benefit/risk. The findings in the RECORD 1 study were favorable for rivaroxaban in regard to occurrence of proximal VTE. Efficacy was demonstrated on the primary endpoint, as well as the main secondary efficacy endpoint of Major VTE. Venographically detected VTE is a surrogate endpoint and has been used for approval of other anticoagulant products for the indications. The Division commented that the venographic evidence of efficacy may provide a sufficient number of events to allow a meaningful statistical comparison. Two of the RECORD studies did not compare rivaroxaban treatment to an approved dose or duration of the comparator. The panel suggested that data from these two studies should not be used in a pooled analysis of treatment effect. The panel noted that when approval is based on a non-clinical endpoint, such as venography, a price is paid with bleeding, a clinical outcome.

After the statistical presentation, the panel inquired about the seven potential Hy's law cases in the enoxaparin control arm. FDA liver experts expressed that not all cases show a signal for liver injury and it is difficult to rule out viruses, alcoholism, and other factors. It requires a thorough review and adjudication which FDA has not been able to do. FDA discussed a recently received adverse event that would require more information.

The panel inquired why follow-up and monitoring of international normalized ratios (INRs) was not necessary. The panel asked for the justification for that. The Division responded that the sponsor did not propose a routine monitoring plan and that routine monitoring was not done in the studies. Also, it is difficult to monitor anti-Factor Xa levels since there is not an accepted standard for the test between institutions. The panel asked how comfortable the Division was with the dose. Clinical Pharmacology noted that it had reviewed safety and efficacy data from phase 2 dose response studies and found a shallow dose response curve for efficacy while a steep dose-response was observed in regard to bleeding, giving support to the selection of a 10mg dose, except for certain special populations at risk for increased exposure (e.g., moderate-severe hepatic impairment, strong CYP3A4/P-gp inhibitor use). The Division informed the panel that body weight as well as other factors such as age, sex, and ethnicity were studied and not deemed to result in clinically relevant exposure changes.

The Division continued its presentations.

Question 1

The Advisory Committee voted 15 to 2 that the "available" clinical data demonstrated a favorable rivaroxaban risk-benefit profile. This vote followed the sponsor's presentation of favorable "liver test" data from the recently completed "ATLAS TIMI 46 Study," for which the Division has received only the study's summary "liver test" data. The Division plans to recommend a Complete Response letter requesting the final ATLAS TIMI 46 study report as well as adjudication of the potential "Hy's cases" in the on-going atrial fibrillation studies. Do you agree?

The panel restated the first question as "Is a signal in short-term data enough to request long-term data before approving a short term indication?"

The panel agreed that the Division is entitled to these data and advised that the Division characterize the potential signal for liver injury. The panel stated that although it does not take 30 days to get liver injury, the Division needs to better characterize the risk; the Division should be able to review the data. The Panel recommended that subjects from the on-going atrial fibrillation studies who had safety issues and stopped medication should be unblinded.

The panel asked if genetic testing was done on the patients. The Division responded that samples were drawn for genetic testing in the Phase 3 studies, but were not analyzed. The Division noted that in its review, it plans to suggest the applicant consider an evaluation of candidate single nucleotide polymorphisms (SNPs) or haplotypes for pharmacogenomic analysis. The panel suggested that the sponsor analyze them as part of the evaluation of potential "Hy's cases."

Question 2

Is completion and full reporting of the "long term, atrial fibrillation" studies essential to assess rivaroxaban's risks and benefits for the "short term" VTE prophylaxis indication?

The panel asked what the rush was to approve rivaroxaban when it is not a priority application. The study data (from ATLAS and Hy's cases from ROCKET) would not take long to review. The Division noted that the ROCKET atrial fibrillation data would not be available until next year; however, the sponsor should be able to unblind the Hy's law cases and submit the data.

The panel recommended a sequential stepwise approach for the decision based on what is observed from the potential "Hy's cases" and ATLAS TIMI 46 Study.

Question 3

The Division regards the pooling of "clinical outcomes" from the four RECORD studies as inappropriate for hypothesis testing because of important differences in the study designs and analytical deficiencies. Do you agree?

The panel generally regarded the pooling as inappropriate and reminded the Division that FDA has set a high standard in regard to comparative efficacy claims. Regardless of how the studies are combined, it is after the fact and FDA has never allowed sponsors to combine studies to make claims.

SUMMARY OF ADVICE:

- The panel agreed that the Division is entitled to the final ATLAS TIMI 46 study report as well as adjudication and unblinding of the potential "Hy's cases" in the on-going atrial fibrillation studies to characterize the potential signal for liver inquiry signal. The panel recommended a sequential stepwise approach for the decision based on what is observed from the potential "Hy's cases" and ATLAS TIMI 46 Study.
- The pooling of "clinical outcomes" from the four RECORD studies for hypothesis testing is inappropriate.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- None

ACTION ITEMS:

- None

ATTACHMENTS/HANDOUTS:

- Division Slides

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Rivaroxaban, NDA 22-406
Johnson and Johnson, Inc.

Oral anticoagulant for use in the prevention of VTE among patients undergoing hip or knee surgery

Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
May 1, 2009

1

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Background

- Warfarin: approved in 1954
- Ximelagatran:
  - "Short term" & "long term" indications
  - Liver toxicity in "long term" studies
  - NA in US; marketing ceased in non-US
- Rivaroxaban:
  - no structural similarity to ximelagatran
  - for only "short term" initial marketing
  - no dose titration, no coag monitoring

2

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

March 19, 2009 AC

- Efficacy: statistical success in 4 studies, mainly on venographic outcomes
- Safety:
  - bleeding
  - potential liver toxicity
  - "long term" study data importance
- Sponsor presented summary "liver" data from a recently completed study
- Favorable AC recommendation based on "available data"

3

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Post-AC

- Unresolved:
  - CMC
  - DSI
- CR Letter anticipated

4

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Panel Questions

1. Do you agree with planned data request?
   - *Final report of study presented at AC*
   - *Adjudication of possible "Hy's cases" in long term studies*
2. Discuss role of "off-label, long term" considerations in "short term" risk-benefit assessment
3. Discuss the company's plan to "pool" data from 4 studies to make a labeling claim of "clinical benefit"

5

Overview: Rivaroxaban for Thromboprophylaxis in Patients Undergoing Hip or Knee Replacement Surgery

Kathy Robie Suh, M.D., Ph.D.
Division of Medical Imaging and Hematology Products
CDER Regulatory Briefing

May 1, 2009

1

FDA Presentations

- **Background for the application**
  - **Kathy Robie Suh, M.D., Ph.D., OODP**
- **Rivaroxaban Efficacy and Safety**
  - **Min Lu, M.D., OOPD**
- **Statistical analysis aspects**
  - **Qing Xu, Ph.D., OB, DBV**
- **Hepatotoxicity Concerns**
  - **Kate Gelperin, M.D., OSE**

2

Thromboprophylaxis in Orthopedic Surgery

- **~ 800,000 patients in US undergo Hip or knee replacement (2005 AAOS statement)**
- **VTE rate ~ 40-60% without prophylaxis**
- **Symptomatic PE or death very uncommon**
- **Imaging endpoints in clinical trials**
- **Proximal DVT generally more important than distal DVT**

3

Drugs Approved for VTE Prophylaxis in Hip and/or Knee Surgery Patients

Drug	Indication	Treatment Duration
Enoxaparin	Hip & Knee	7 to 10 days
	Hip, extended prophylaxis	35 days
Dalteparin	Hip	5 to 10 days
Fondaparinux	Hip & Knee	5 to 9 days

4

Considerations for Evaluation of Rivaroxaban for Thromboprophylaxis in Major Orthopedic Surgery

- **Efficacy:**
  - **Imaging (venography) endpoints accepted**
  - **Missing data common (~ 30%)**
- **Safety:**
  - **Enoxaparin and liver test abnormalities**
  - **"Fixed" dose & "special populations"**
- **Regulatory:**
  - **Drugs currently available, all parenteral**
  - **First oral anticoagulant since warfarin**
  - **Potential "extended prophylaxis" or other use**
  - **On-going studies assess extended use**

5

Rivaroxaban
NDA 22-406

Min Lu, M.D., M.P.H.
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
FDA
May 1, 2009

Review Questions

- Efficacy
  - Do the data show efficacy?
- Safety
  - Does rivaroxaban increase bleeding?
  - Does rivaroxaban increase the risk for hepatotoxicity?
  - Are ongoing studies important for the current application?

- Indication:
  - "for the prophylaxis of DVT and PE in patients undergoing:
  - hip replacement surgery
  - knee replacement surgery."
- Dosing regimen:
  - 10 mg orally, once daily
    - 35 days for hip replacement
    - 14 days for knee replacement

Clinical Development Program

- Prophylaxis of DVT/PE in hip or knee surgery
- Prophylaxis of DVT/PE in hospitalized, medically ill
- DVT/PE secondary prevention
- Atrial fibrillation
- Acute coronary syndrome

On-Going

Clinical Development Program

- ~ 18,000 patients in 64 completed studies
- Four RECORD Studies:
  - main data source
  - 12,729 patients in 41 countries
- Ongoing studies:
  - Limited, preliminary information
  - Six month update:
    - ~ 10,000 exposed for one month
    - ~ 6,000 exposed for six months

RECORD Studies

- RECORD 1 & 2: hip
- RECORD 3 & 4: knee
- Randomized (1:1) to rivaroxaban or enoxaparin, double-blind, international
- Venography on Day 12 (knee) or Day 35 (hip)
- Follow-up for one additional month
- Central adjudication of major outcomes

Efficacy Considerations

- **RECORD 3:**
  - used unapproved lower enoxaparin dose for knee: 40 mg daily dose
  - potential for under-estimation of enoxaparin effect
- **RECORD 2:**
  - rivaroxaban for 35 days
  - enoxaparin for only 12 days
  - potential for under-estimation of enoxaparin effect

Primary Efficacy Endpoint: RECORD 1 & 2 (hip)

	RECORD 1		RECORD 2	
	Riva n = 1595	Enox n = 1558	Riva n = 864	Enox n = 869
"Total VTE"	18 (1.1%)	58 (3.7%)	17 (2.0%)	81 (9.3%)
Components (numbers of patients with outcome)				
All Death	4	4	2	6
N-F PE	4	1	1	4
Prox DVT	1	31	5	44
Distal DVT	12	27	11	49

p < 0.001 in RECORD 1 and 2

Primary Efficacy Endpoint: RECORD 3 & 4 (knee)

	RECORD 3		RECORD 4	
	Riva n = 824	Enox n = 878	Riva n = 965	Enox n = 959
"Total VTE"	79 (9.6%)	166 (18.9%)	67 (6.9%)	97 (10.1%)
Components (numbers of patients with outcome)				
All Death	0	2	2	3
N-F PE	0	4	5	8
Prox DVT	9	20	8	14
Distal DVT	74	156	57	82

p < 0.001 in RECORD 3 and p<0.05 in RECORD 4

Symptomatic VTE (DVT or PE)
in RECORD Study Safety Population

RECORD	Riva	Enoxa	Hazard ratio (95% CI)
1	6/2209 (0.3%)	11/2224 (0.5%)	0.5 (0.2, 1.5)
2	3/1228 (0.2%)	15/1229 (1.2%)	0.2 (0.1, 0.7)
3	8/1220 (0.7%)	24/1239 (1.9%)	0.3 (0.2, 0.8)
4	11/1526 (0.7%)	18/1508 (1.2%)	0.6 (0.3, 1.3)

Safety Results

- Overall Adverse Events
- Bleeding Events
- Hepatic Events

Adverse Events in RECORD Studies

Adverse events	Riva n =6183	Enoxa n =6200
Any AEs	4179 (67.6%)	4306 (69.5%)
Death	13 (0.2%)	25 (0.4%)
Any SAEs	406 (6.6%)	528 (8.5%)
AE resulting in permanent discontinuation of study drug	230 (3.7%)	288 (4.7%)

Deaths (treatment and follow-up) *in RECORD Study*

RECORD	Riva	Enoxa or Enoxa/placebo
1 (hip)	5/2209 (0.2%)	5/2224 (0.2%)
2 (hip)	2/1228 (0.2%)	8/1229 (0.7%)
3 (knee)	0/1220 (0.0%)	6/1239 (0.5%) (40 mg od)
4 (knee)	6/1526 (0.4%)	6/1508 (0.4%)

5/12/2009 13

"Major Bleeding" in RECORD Studies

Event	Riva n = 6183	Enoxa n = 6200
"Major bleeding"	24 (0.4%)	13 (0.2%)
Components (numbers of patients)		
Fatal	2	0
Bleeding into critical organ	3	5
Bleeding requiring re-op	12	7
Extra-surgical site bleeding with > 2 g/dL Hgb decrease	8	1
Extra-surgical site bleeding with > 2 units blood	8	1

5/12/2009 14

"Non-major" Bleeding in RECORD Studies

Events	Riva n = 6183	Enoxa n = 6200
Any bleeding	434 (7.0%)	401 (6.5%)
"Clinically relevant" non-major bleeding	177 (2.9%)	145 (2.3%)
Other non-major bleeding	260 (4.2%)	256 (4.1%)

5/12/2009 15

Possible Signal for Liver Toxicity in RECORD Studies

Small imbalance in:

- Serious hepatic events
- ALT and TB marker:

(ALT > 3X ULN and TB > 2X ULN)

5/12/2009 16

Incidence of ALT > 3x ULN Concurrent With TB >2x ULN in RECORD Studies

Result	Rivaroxaban (n=6131)	Enoxaparin (n=6131)
ALT >3xULN with TB >2xULN	9 (0.15%)	7 (0.11%)
Drug-relatedness Assessment by LAP (n)*		
Unrelated/excluded	2	4
Possible	6	2
Probable	1	1
Definite	0	0

* "most relatedness" assignment by any adjudicator

5/12/2009 17

Incidence of ALT/TB Elevations in RECORD Studies

Result	Riva n = 6131	Enoxa n = 6131
ALT > 3x ULN	2.5%	3.7%
> 5x ULN	0.9%	1.3%
> 8x ULN	0.3%	0.3%
> 10x ULN	0.16%	0.15%
> 20x ULN	0.03%	0.02%
TB > 1.5x ULN	2.8%*	2.6%
> 2x ULN	0.8%*	0.8%

*n = 6133

5/12/2009 18

Incidence of Serious "Hepatic" Adverse Events in RECORD Studies

Preferred term	Riva n =6183	Enoxa n = 6200
Any event	33 (0.5%)	27 (0.4%)
ALT increased	17 (0.3%)	11 (0.2%)
AST increased	5 (0.1%)	7 (0.1%)
Bilirubin increased	5 (0.1%)	4 (0.1%)
"Hepatic enzyme increased"	6 (0.1%)	7 (0.1%)

Incidence of ALT > 3x ULN Concurrent With TB >2x ULN in Phase 2 and 1 Studies

Result	Riva N = 3206	Enoxa n = 847
ALT >3xULN with TB >2xULN	5 (0.16%)	2 (0.24%)
"Liver-related deaths"	2 (0.06%)	0 (0.00%)

Ongoing Studies (as 12/5/08)
ALT >3x ULN Concurrent With TB>2x ULN

Ongoing Studies	Rivaroxaban	Control
ATLAS ACS TIMI 46	0/2270	3/1134
EINSTEIN DVT/PE	3/1562	0/1549
ROCKET-AF	16 (13 blinded, 3 warfarin)/10,472	
J-ROCKET-AF (as 10/30/08)	3 (2 blinded, 1 rivaroxaban)/1,108	
MAGELLaN	2 (1 blinded, 1 enoxaparin)/808	
Total	27 Cases (16 blinded)	
"Liver-related deaths"	3-blinded, 2-rivaroxaban, 1-placebo, 1-enoxaparin	

ATLAS ACS TIMI 46 Study

- Randomized, double-blind, placebo-controlled, dose-escalation phase 2 study
- Patients with acute coronary syndrome
- Rivaroxaban doses: 5, 10, 15, and 20 mg
- 1445 (of 2309) received ≥6 months
- Data submitted: summary in 6-month safety update (2/2/2009) and liver dataset for eDISH

ATLAS ACS TIMI 46 Study

Table 3: Incidence of ALT or AST >3x ULN and Total Bilirubin >2x ULN (Subjects Available for Safety in ATLAS ACS TIMI 46)

Laboratory Abnormality Time of Measurement	Rivaroxaban N=2302 n/J (%)	Placebo N=1149 n/J (%)
ALT >3x ULN total bilirubin >2x ULN		
Baseline	0/2215 (0.0%)	0/1103 (0.0%)
Postbaseline	0/2270 (0.0%)	3/1134 (0.3%)
Treatment-emergent	0/2172 (0.0%)	2/1082 (0.2%)
AST >3x ULN, total bilirubin >2x ULN		
Baseline	2/2120 (0.1%)	1/1054 (0.1%)
Postbaseline	1/302 (0.3%)	4/162 (2.5%)
Treatment-emergent	1/231 (0.4%)	3/131 (2.3%)

ATLAS ACS TIMI 46 Study

Table 2: Incidence of Treatment-Emergent Abnormal Liver Function Test (ALT and Total Bilirubin) Values (Subjects Available for Safety in ATLAS ACS TIMI 46)

Laboratory Variable Level of Increase	Rivaroxaban N=2302 n/J (%)	Placebo N=1149 n/J (%)
ALT		
>3x ULN	55/2093 (2.6%)	37/1056 (3.5%)
>5x ULN	12/2137 (0.6%)	12/1076 (1.1%)
>8x ULN	2/2146 (0.1%)	3/1079 (0.3%)
>10x ULN	1/2148 (<0.1%)	2/1079 (0.2%)
>20x ULN	0/2148 (0.0%)	0/1079 (0.0%)
Bilirubin, total		
>1.5x ULN	17/2149 (0.8%)	11/1084 (1.0%)
>2x ULN	5/2163 (0.2%)	4/1090 (0.4%)
>3x ULN	0/2166 (0.0%)	0/1092 (0.0%)
>5x ULN	0/2166 (0.0%)	0/1092 (0.0%)
>8x ULN	0/2166 (0.0%)	0/1092 (0.0%)

Review Questions

- Do the data show efficacy?
  - Yes, based on "Total VTE"
- Does rivaroxaban increase bleeding?
  - Yes
- Does rivaroxaban increase the risk for hepatotoxicity?
  - Cannot exclude possibility
- Are ongoing studies important for the current application?
  - Yes. ATLAS study and Hy's law cases in ROCKET studies.

5/12/2009 25

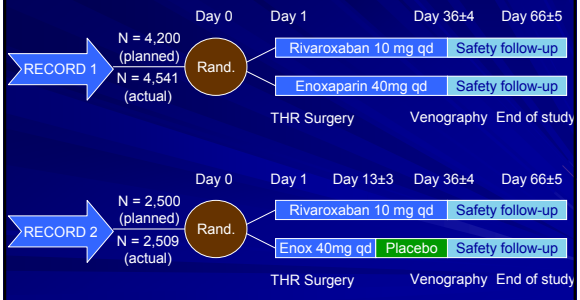
Rivaroxaban, NDA 22-406 Regulatory Briefing

Qing Xu, Ph.D.
Office of Biostatistics, FDA

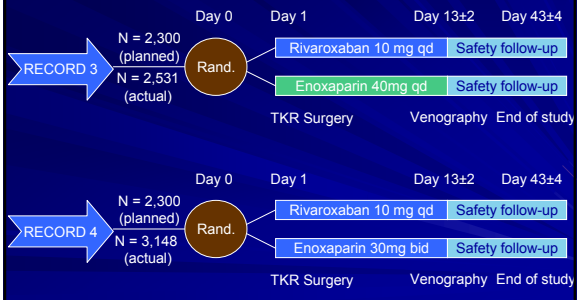
Outline

- Brief Description of Clinical Development Program
- Integrated Analyses
  - Benefit
  - Bleeding Risk

Record 1 & 2 Study Design-THR



Record 3 & 4 Study Design-TKR



Results

- Statistical superiority for Rivaroxaban achieved at 5% level
  - For the primary endpoint of "Total VTE"
  - Primarily due to venography based components
  - Low rates of Death and Non-fatal PE
    - Effect of Rivaroxaban on these is unclear
- SAP did not include control of false positive rate for mul iple secondary endpoints for anticipated claims based on statistical significance
- Nominal p-values for secondary endpoints
  - < 0.05 ONLY for RECORD 2 and 3, NOT for RECORD 1 and 4
  - Supportive of primary analysis

Agreement

The data from RECORD studies demonstrate efficacy of Rivaroxaban for prophylactic anticoagulation after THR/TKR surgery

What is Extent of Benefit

An Evaluation

7

Symptomatic VTE or Death

- Clinically Important Endpoint
- No allocation of α in the Statistical Analysis plan for each RECORD study
- Any comparison of rivaroxaban with enoxaparin in terms of this endpoint
  - exploratory
  - at best hypothesis-generating

8

Symptomatic VTE (DVT or PE)
in RECORD Study Safety Population

RECORD	Riva	Enox
1 (hip)	6/2209 (0.3%)	11/2224 (0.5%)
2 (hip) (Short Enox Duration)	3/1228 (0.2%)	15/1229 (1.2%)
3 (knee) (Lower Enox dose)	8/1220 (0.7%)	24/1239 (1.9%)
4 (knee)	11/1526 (0.7%)	18/1508 (1.2%)

9

Integrated Analyses

- Prospective plan – Simple pooling
- Important study characteristics are ignored
  - Type of surgery
  - Dose
  - Duration
- No Strong control of Type I error
  - not built into the plan for pooled analyses for anticipated claims based on statistical significance.
- This type of analysis can yield spurious results.

10

Sponsor's Results for Symptomatic VTE or Death (*In RECORD Study Safety Population*)

RECORD	Riva	Enox	Hazard ratio (95% CI)
1	10/2209 0.45%	15/2224 0.67%	0.7 (0.3, 1.5)
2 (Shorter treatment duration for Enox)	5/1228 0.41%	20/1229 1.6%	0.2 (0.1, 0.7)
3 (unapproved dose regimen for Enox)	8/1220 0.66%	26/1239 2.1%	0.3 (0.1, 0.7)
4	12/1526 0.79%	21/1508 1.4%	0.6 (0.3, 1.2)
Pooled	35/6183 0.57%	82/6200 1.3%	0.4 (0.29, 0.63)

11

Statistical Methods Used by FDA Integrated Analysis

- **Meta-Analysis**
  - Provides ability to control between-study variation
  - Provides more precise estimate of the overall treatment effect
- **Proportional Hazard Regression adjusted for covariates**
  - Enables adjustment for the covariates or risk factors
  - Gives more precise analysis
  - Increases model power

12

FDA : Symptomatic VTE adjust covariate

Study	Hazard Ratio	95% CI	P-value
Record 1 (age surgery)	0.67	(0.30, 1.49)	0.32
Record 2 (age surgery)	0.25	(0.09, 0.67)	0.0055
Record 3	0.309	(0.14, 0.68)	0.0037
Record 4	0.564	(0.28, 1.15)	0.11
Pooled 1 & 4 (treatdur, study)	0.67	(0.39, 1.15)	0.143
Pooled (treatdur, study, age)	0.69	(0.46, 1.04)	0.07
Record 2 (Day 15) (age, surgery)	0.27	(0.06, 1.30)	0.10 (0.18)*

13

Meta Analysis for Symptomatic VTE or Death for Pooled 1 & 4 Study

Study name	Hazard ratio	Lower limit	Upper limit	Z Value	p Value
RECORD 1	0.670	0.301	1.493	-0.979	0.327
RECORD 4	0.564	0.277	1.147	-1.581	0.114
	0.608	0.358	1.035	-1.833	0.067

Statistics for each study

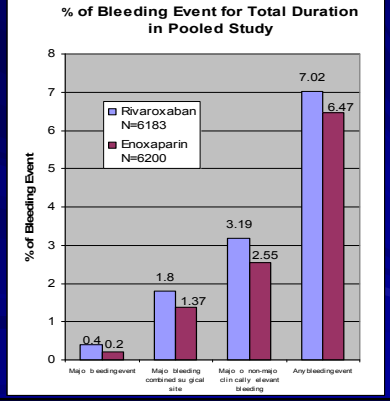
Hazard ratio and 95% CI

Meta Analysis

Bleeding Risk

An Evaluation

15



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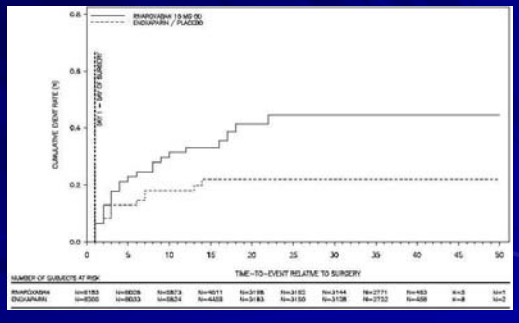
Cumulative Rate of Major Bleeding Events – Pooled Study

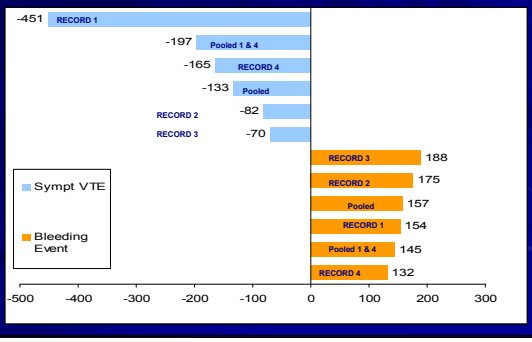


17

Benefit & Risk

Number needed to treat -Symptomatic VTE

Number needed to harm-Major or Non-major clinically relevant bleeding



Benefit/Risk

- Evidence of efficacy of Rivaroxaban for anticoagulation prophylaxis
  - In terms of Total VTE
- No evidence of superiority of Rivaroxaban compared to Enoxaparin
  - For “Symptomatic VTE or Death”
- Consistent evidence of increased risk of bleeding for Rivaroxaban compared to Enoxaparin

19

Ongoing Evaluation of Potential Severe Liver Injury Signal in Rivaroxaban Clinical Trials

FDA / CDER Regulatory Briefing
May 1, 2009

Kate Gelperin, M.D., M.P.H.
Division of Epidemiology
Office of Surveillance and Epidemiology

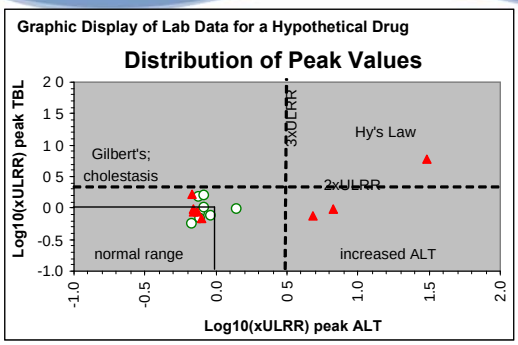
Severe Liver Injury

- Defined in this review as ALT >3xULN *and* TBL >2xULN
- Rationale:
  - ALT (alanine aminotransferase) is a sensitive test for severe liver injury but poorly specific
  - Evaluating concurrent TBL (total bilirubin) improves specificity and increases positive predictive value for serious outcomes

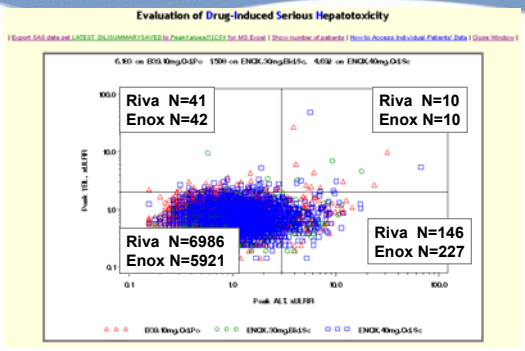
"Hy's Law" – severe liver injury

- Instances (even very few of them) of transaminase elevation accompanied by elevated bilirubin (even if obvious jaundice was not present) have been associated with, and have often predicted, post-marketing serious liver injuries (fatal or requiring transplant)*
- Estimated mortality at least 10%
- Explanation: hepatocellular injury great enough to interfere with bilirubin excretion (in the absence of biliary obstruction) involves a large fraction of the liver cell mass

* Zimmerman HJ. Drug-induced liver disease. In: Hepatotoxicity The Adverse Effects of Drugs and Other Chemicals on the Liver. Appleton-Century-Crofts, New York, 1978, 1999.



Slide and graphic concept courtesy Dr. John Senior



Lab Data **RECORD 1-4**: rivaroxaban (N=6183) vs. enoxaparin (N=6200)
Slide courtesy Dr. Ted Guo

Enoxaparin Labeling

- Approved: March 29, 1993
- Labeled liver events: Asymptomatic increases in ALT greater than 3 times upper limit of normal have been reported in 5.9% of patients
- Elevations revers ble and rarely associated with bilirubin increases*

* LOVENOX (enoxaparin sodium injection) prescribing information (May 2008, sanofi-aventis)

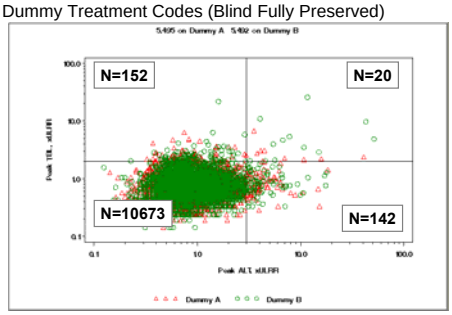
LAP* Causality Assessments for Potential "Hy's Law" Cases in RECORD 1-4

- Rivaroxaban
  - Total with concurrent increased ALT >3xULN and TBL >2xULN = 9 cases
  - Possibly related to drug (LAP) = 7 cases
- Enoxaparin
  - Total with concurrent increased ALT >3xULN and TBL >2xULN = 7 cases
  - Possibly related to drug (LAP) = 3 cases

* **LAP** (Liver Advisory Panel) is the Sponsor's expert hepatology panel

7

Lab Data from Ongoing Blinded **ROCKET** (Atrial Fibrillation) Study wi h Dummy Treatment Codes (Blind Fully Preserved)



Slide courtesy Dr. Ted Guo

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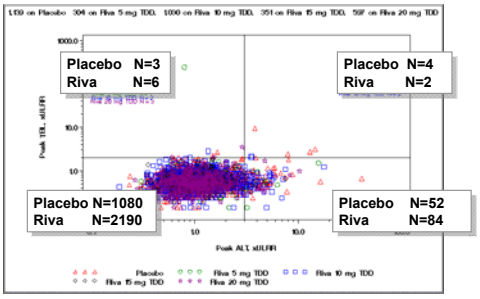
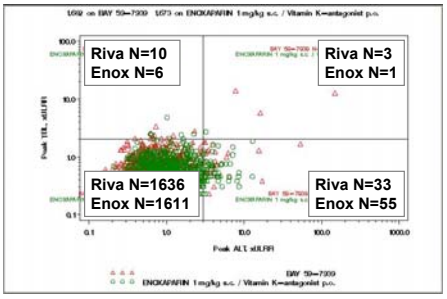
Lab Data from **ATLAS** (ACS) Study



Slide courtesy Dr. Ted Guo

9

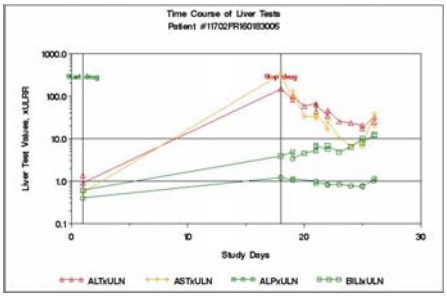
Lab Data from Long-Term Open Label Study **EINSTEIN** DVT/PE



Slide courtesy Dr. Ted Guo

10

Fatal case wi h liver injury and heart failure from **EINSTEIN** study



Slide courtesy Dr. Ted Guo

11

FDA Experience with Hepatotoxins "Hy's Law" with Troglitazone

In the Troglitazone NDA database (n=2510):

- No cases of liver failure
- 1.9% of patients had ALT >3x ULN
- 0.2% (5 pa ients) had ALT >30x ULN (two wi h jaundice) » "Hy's Law" cases in retrospect

12

FDA Experience with Hepatotoxins "Hy's Law" with Troglitazone

- Drug was withdrawn from US market in March 2000
  - FDA reviewed 94 cases of drug-induced liver failure received postmarketing *
  - Progression to irreversible liver injury occurred within less than one month interval in 19 of these patients
- Casts doubt on the value of monthly monitoring in setting of rapid liver injury

* Graham DJ, Green L, Senior JR, Nourjah P. Troglitazone-induced liver failure: a case study. Am J Med 2003; 114: 299-306.

13

FDA Experience with Hepatotoxins "Hy's Law" with Ximelagatran

- Anticoagulant (direct thrombin inh bitor) developed for similar indications as rivaroxaban
- Severe liver injury in long-term trials:
  - Ximelagatran 37/6948 (0.5%)
  - Warfarin 5/6230 (0.08%)
  - Relative risk 6.6
- No signal for severe liver injury seen in short-term trials but strong signal in long-term trials for stroke prevention in atrial fibrillation patients

14

FDA Experience with Hepatotoxins "Hy's Law" with Ximelagatran

- Initial signs of liver injury within first 30 days for six study subjects in LT trials who went on to develop severe liver injury
- Drug not approved in the US
- Later, sponsor decided to withdraw drug from worldwide marketing

15

OSE Conclusion and Recommendation

- A potential signal for severe liver injury with rivaroxaban has not been fully characterized at this time.
- Complete assessment, fully evaluating pertinent safety data from long term clinical trials, should be undertaken.

16

Acknowledgments

- DMIHP colleagues
- John Senior, MD
- Ted Guo, PhD
- Mark Avigan, MD, CM
- Allen Brinker, MD, MS
- Solomon Iyasu, MD, MPH
- Kathryn O'Connell, MD, PhD
- Gerald Dal Pan, MD, MHS

17

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/s/

Kathy Robie-Suh

5/14/2009 02:32:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Andrea F. Kollath DVM Director, Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300
Raritan, NJ 00869-0602

Dear Ms. Kollath:

Please refer to your new drug application (NDA) dated August 13, 2008, submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for XARELTO.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and found the Drug Master Files 21580, 21581, and 21592 rivaroxaban to be inadequate to support the NDA. Communications detailing the deficiencies have been issued to the designated agents.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Sarah Pope

5/1/2009 10:21:03 AM

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE:	April 29, 2009
APPLICATION NUMBER:	NDA 22-406

BETWEEN:

Name:	Andrea F. Kollath, DVM, Director, Regulatory Affairs
e-mail:	AKollath@its.jnj.com
Representing:	Johnson and Johnson Pharmaceutical Research and Development

AND

Name:	Marcus Cato, M.B.A., Regulatory Project Manager Division of Medical Imaging and Hematology Products HFD-160

SUBJECT:	Pharmacology/Toxicology information

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, April 29, 2009 8:08 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Importance: High

Dear Andrea,

We request that you submit the following Pharmacology/Toxicology information on or before April 30, 2009.

Please provide the primary study sources of these dose multiples:

"Reproduction studies have been performed in rats and rabbits at exposure levels up to 40 (rat) and 94 (rabbit) times the therapeutic exposure levels based on unbound AUC in humans at a rivaroxaban dose of 10 mg/day."

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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/s/

Marcus Cato
4/30/2009 04:01:46 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the meeting between representatives of your firm and the FDA on April 24, 2009. The purpose of the meeting was to discuss some discrepancies noted in the pooled statistical analysis.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	April 24, 2009
TIME:	10:00 AM - 11:00 AM EST
LOCATION:	CDER WO conf Rm 1311, Bldg 22
APPLICATION:	NDA 22-406
SPONSOR:	Johnson and Johnson Pharmaceutical Research and Development (J&J)
DRUG NAME:	Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING:	Type C, Guidance, Statistics

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., Clinical Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader
Aloka G Chakravarty, Ph.D., Director

OFFICE OF BIOSTATISTICS

Ram Tiwari, Ph.D., Associate Director

EXTERNAL ATTENDEES:

JOHNSON & JOHNSON

Gary Peters, MD Franchise Medical Leader
Lloyd Haskell, MD, Compound Development Team leader
Leonard Oppenheimer, PhD. Statistical Sciences
John Zhang PhD. Statistical Sciences
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Kollath, DVM, Regulatory Affairs

BAYER

Martin Homering Statistical Sciences
Torsten Westermeier PhD Therapeutic Area Expert Statistician
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology

BACKGROUND:

The appropriateness of the pooled statistical analysis of the four RECORD studies was discussed at the March 19, 2009 Advisory Committee (AC) meeting. The sponsor and FDA agreed to meet to discuss some discrepancies in the pooled statistical analyses in greater detail.

MEETING OBJECTIVES:

To discuss the discrepancies observed in the pooled statistical analyses between the sponsor and FDA.

DISCUSSION POINTS:

J&J presented slides (see attached).

Slides 1-8

J&J expressed concern regarding the FDA AC presentations and stated that it does not regard the FDA derived hazard ratio of 3.92 for the RECORD 2 major or non-major clinically relevant bleeding events adjusting duration of treatment as an accurate representation. J&J does not believe that adjusting for treatment duration provides the best representation as treatment duration confounds the treatment effect.

FDA emphasized that the impact of these types of analyses on labeling may be moot because whether using the sponsor's hazard ratio of 1.2 or using the FDA ratio of 3.92 both are statistically significant and point to a concern for bleeding. FDA does not expect to have comparative safety and/or efficacy claims in the label (ie., direct claims of comparative effects between rivaroxaban and enoxaparin). FDA further emphasized that point estimates from any modeling are not anticipated for the labeling.

Slides 9-17

J&J expressed similar concern regarding the FDA AC presentations on the pooled symptomatic venous thromboembolism (VTE) or death analyses.

FDA stated that the sponsor submitted statistical analysis plan was submitted prior to unblinding RECORD 4 but after RECORD 1-3 had been unblinded. FDA emphasized the exploratory nature of this pooled analysis, as stated in the plan. J&J stated that, based on the statement of objective, the plan for hypothesis testing was implied. FDA advised that when the results of 3 studies were available (prior to finalization of the analytical plan) it is difficult to then say that the final pooled analysis was a confirmatory analysis. FDA continues to regard the pooled (symptomatic VTE) analysis as exploratory as it lacked a clearly stated hypothesis. FDA

emphasized that it does not disapprove of J&J examining the data in subsequent pooling analysis, in an exploratory manner to help understand the totality of the data. However, drawing conclusions to propose certain claims is inappropriate, based on exploratory analyses. J&J reminded the agency that it is not seeking a superiority claim (compared to enoxaparin).

DECISIONS (AGREEMENTS) REACHED:

- FDA continues to regard the pooled analyses of "symptomatic VTE" as exploratory in nature. FDA acknowledges multiple approaches to summarizing the bleeding data. Considerations for labeling will depend upon multiple factors, including the clinical importance of analytical findings, the analytical methods and the best approach to describing important clinical information.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- None

ACTION ITEMS:

- None

ATTACHMENTS/HANDOUTS:

- J&J submitted slides

NDA 22-406
Rivaroxaban

April 24, 2009
Biostatistics Meeting
J&J/Bayer

Purpose of Meeting

1. Reconcile currently identified differences
   - AdCom bleeding results
   - AdCom symptomatic VTE or death results
   - Pooling strategy
2. Identify any new differences
3. Identify any new requests

Agenda

Reconcile Differences

- Pooled bleeding analysis (Question 2c ii)
- Pooled symptomatic VTE or death analysis (Questions 1c, 1d and 1e)
- Validity of Sponsor's pooling strategy (Questions 1a and 1b)
- FDA BD multiple bleeds (Question 2c i)
- Other differences (Question 2a)

New requests (Question 2b)

Pooled bleeding analysis (Question 2c ii)

- Take major or non major clinically relevant bleeding events as an example
- RECORD 2
- Pooled RECORD 1-4

Treatment Emergent Major or Non Major Clinically Relevant Bleeding Events Safety Population

STUDY	Rivaroxaban	Enoxaparin	Absolute risk difference† (95% CI)	Hazard ratio (95% CI)
RECORD 1 (THR)	3.17% (70/2209)	2.52% (56/2224)	0.63% (-0.35, 1.61) p = 0.206	1.25 (0.88, 1.78)
RECORD 2‡ (THR)	3.34% (41/1228)	2.77% (34/1229)	0.59% (-0.77, 1.95) p = 0.394	1.20 (0.76, 1.89)
RECORD 3 (TKR)	3.28% (40/1220)	2.74% (34/1239)	0.53% (-0.81, 1.87) p = 0.439	1.19 (0.76, 1.88)
RECORD 4 (TKR)	3.01% (46/1526)	2.25% (34/1508)	0.78% (-0.36, 1.92) p = 0.179	1.34 (0.86, 2.09)

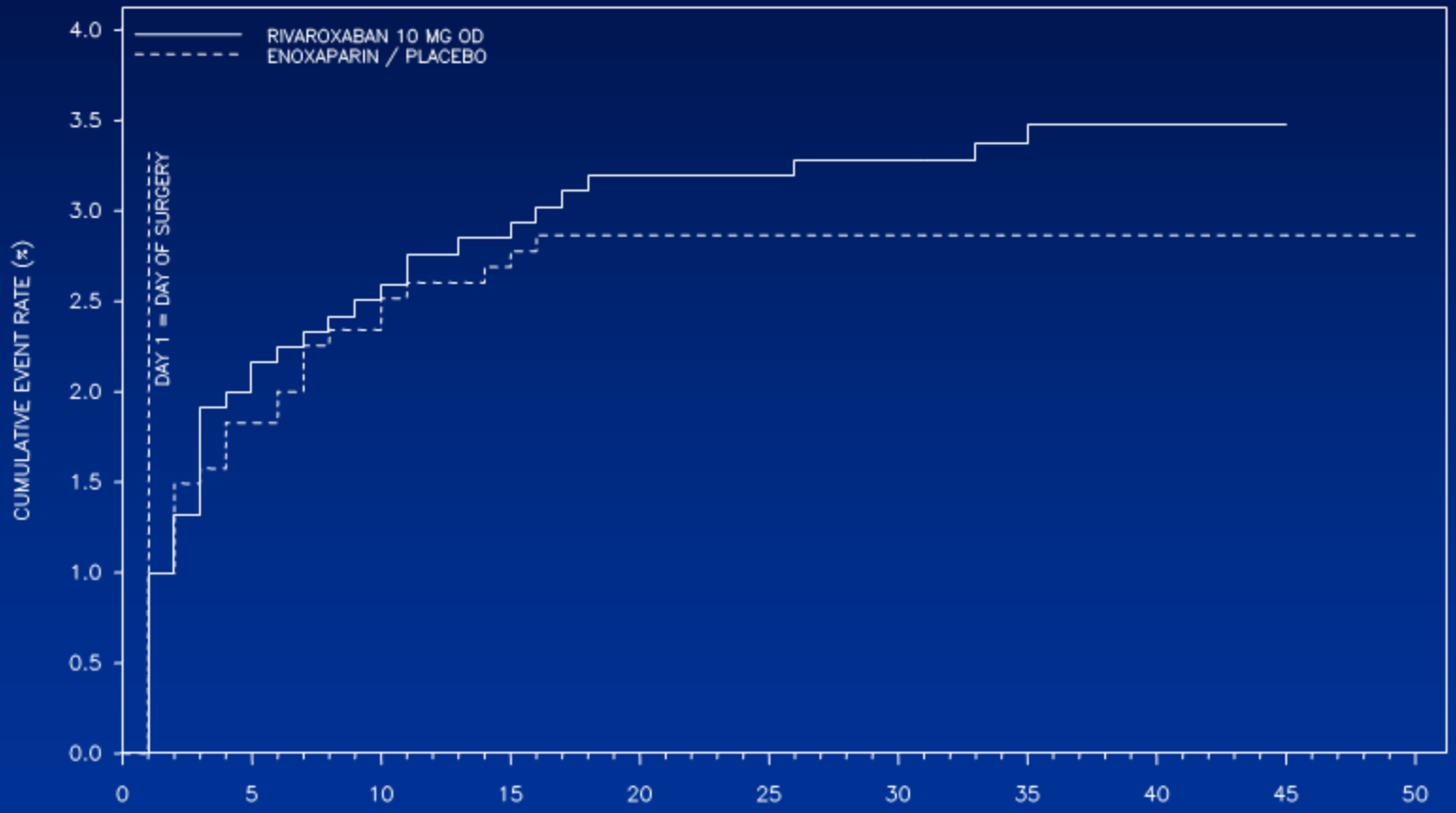
†primary analysis

‡ Active comparator included a placebo control period after day 12

RECORD 2: Major or Non-Major Clin. Relevant Bleeding Events - Safety Population

	Riva	Enox		p-
Pooled Analyses	K/N (%)	K/N (%)	HR (95% CI)	Value
FDA AdCom			3.92 (2.03,7.58)	0.000
Bayer/J&J				
Treatment emergent	41/1228 (3.34)	34/1229 (2.77)	1.20 (0.76, 1.89)	0.432
Adj for Age	41/1228 (3.34)	34/1229 (2.77)	1.20 (0.76, 1.89)	0.429
Until Day 12±2:	34/1228 (2.77)	32/1229 (2.60)	1.06 (0.65, 1.71)	0.821

Treatment Emergent Major or Non-Major Clinically Relevant Bleeding RECORD 2 Safety Population



NUMBER OF SUBJECTS AT RISK

RIVAROXABAN	N=1228	N=1162	N=1134	N=1118	N=1104	N=1099	N=1092	N=963	N=149	N=1	N=0
ENOXAPARIN	N=1229	N=1156	N=1126	N=1111	N=1095	N=1083	N=1074	N=949	N=157	N=3	N=1

FDA Analysis Results for Bleeding

Proportional Hazard Regression Model Adjusted for Covariates

Type of Bleeding	P-value	HR	95% CI
Major or Non-Major Clinically Relevant Bleeding	<0.0001	1.56	(1.2, 1.9)
(sponsor's results)	(0.039)	(1.3)	(1.0, 1.5)
Major Bleeding	0.0037	3.0	(1.4, 6.2)
(sponsor's results)	(0.078)	(1.8)	(0.94, 3.6)
Major Bleeding Incl Surgical Site	0.0035	1.6	(1.1, 2.1)
(sponsor's results)	(0.063)	(1.3)	(1.0, 1.7)
Any Bleeding	0.0226	1.17	(1.0, 1.4)
(sponsor's results)	(0.26)	(1.1)	(0.9, 1.2)

Pooled symptomatic VTE or death analysis (Question 1c)

- RECORD 2
- Pooled RECORD 1-4

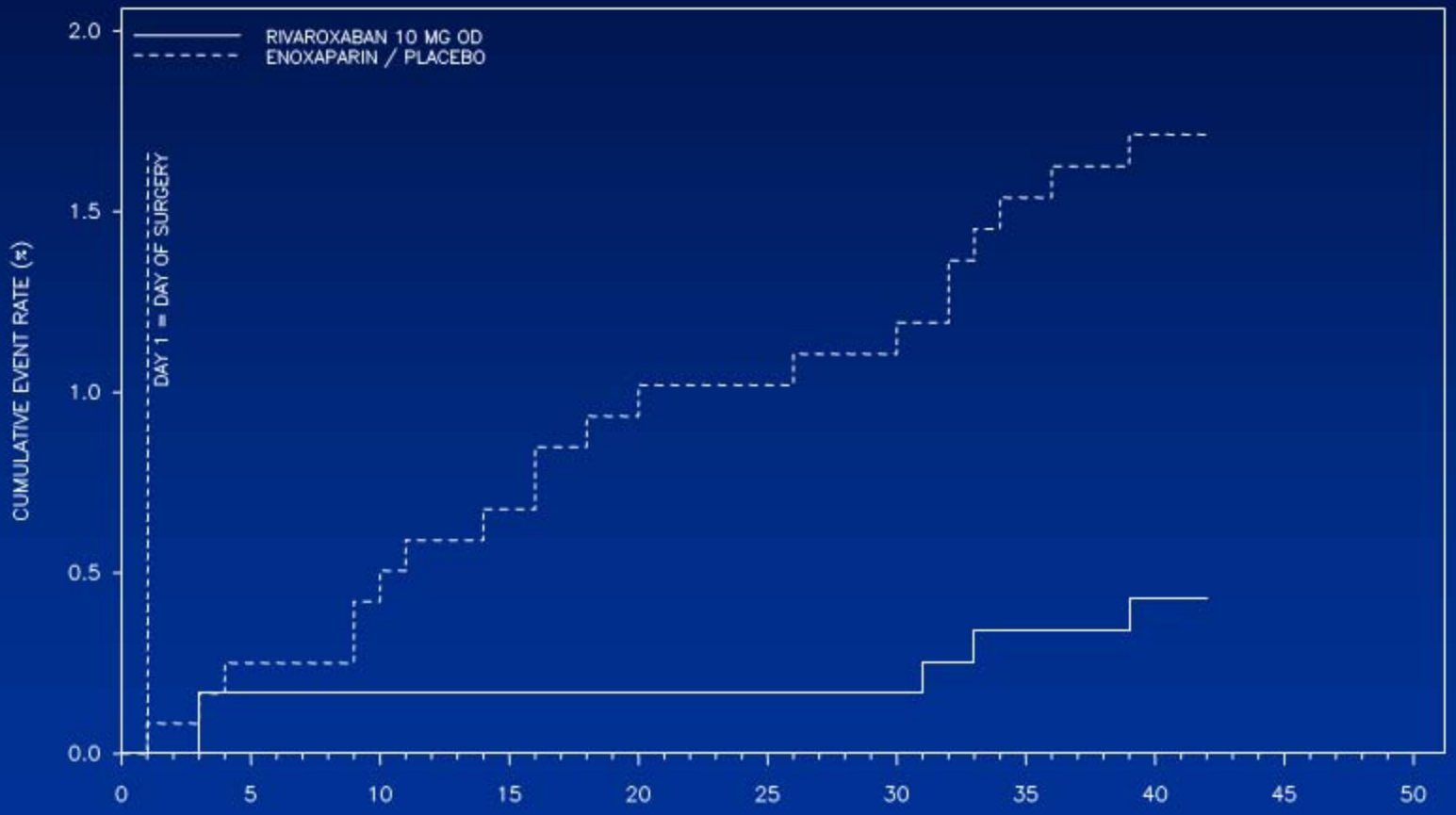
Symptomatic VTE or Death
Treatment Phase
By Study and Pooled Safety Population

Symptomatic VTE or death			Hazard Ratio	
Study	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Pt Estimate	(95% CI)
RECORD 1	10/2209 (0.45)	15/2224 (0.67)	0.67	(0.30, 1.48)
RECORD 2	5/1228 (0.41)	20/1229 (1.63)	0.25	(0.09, 0.66)
RECORD 3	8/1220 (0.66)	26/1239 (2.1)	0.31	(0.14, 0.68)
RECORD 4	12/1526 (0.79)	21/1508 (1.39)	0.56	(0.28, 1.15)
Pooled RECORD 1-2	15/3437 (0.44)	35/3453 (1.01)	0.43	(0.23, 0.78)
Pooled RECORD 3-4	20/2746 (0.73)	47/2747 (1.71)	0.42	(0.25, 0.72)
Pooled RECORD 1-4	35/6183 (0.57)	82/6200 (1.32)	0.42	(0.29, 0.63)

RECORD 2: Symptomatic VTE or death Safety Population

	Riva	Enox	
Pooled Analyses	K/N (%)	K/N (%)	HR (95% CI)
FDA AdCom			2.14 (0.77,5.94)
Bayer/J&J			
RECORD: 2	5/1228 (0.41)	20/1229 (1.63)	0.25 (0.09, 0.66)
RECORD: 2 until Day 12±2	2/1228 (0.16)	5/1229 (0.41)	0.40 (0.08, 2.05)

Symptomatic VTE or Death
RECORD 2 Safety Population



NUMBER OF SUBJECTS AT RISK

RIVAROXABAN	N=1228	N=1191	N=1180	N=1172	N=1166	N=1162	N=1160	N=1140	N=1116	N=0	N=0
ENOXAPARIN	N=1229	N=1184	N=1172	N=1158	N=1152	N=1147	N=1145	N=1133	N=1110	N=0	N=0

Pooled RECORD 1-4: Symptomatic VTE or death Safety Population

	Riva	Enox		p-Value
Pooled Analyses	K/N (%)	K/N (%)	HR (95% CI)	Treat/Inter
FDA AdCom Slide 14			0.65 (0.30,1.44)	0.291
FDA AdCom Slide 15			0.69 (0.46,1.04)	0.07
Bayer/J&J				
Study as covariate	35/6183 (0.57)	82/6200 (1.32)	0.42 (0.29,0.63)	<0.001
Study as strata	35/6183 (0.57)	82/6200 (1.32)	0.43 (0.29,0.63)	<0.001
Until Day 12±2	29/6183 (0.47)	60/6200 (0.97)	0.48 (0.31,0.75)	0.001

Validity of Sponsor's pooling strategy (Question 1a) Pre-specified

Objectives and Rationale for the integrated SAP

- Pre-planned in SAP
- Assessment of clinically relevant, infrequent outcomes
- Components of primary composite endpoints-total VTE
- Consistent with draft "Guidance for Industry: Integrated Summary of Effectiveness, Aug 2008"

Efficacy Endpoints

- Symptomatic VTE or death

Safety Endpoints

- Adjudicated bleeding events
- Liver function lab tests

Validity of Sponsor's pooling strategy (Question 1b) Multiplicity Adjustment

- Symptomatic VTE/Death: low incidence (component of composite of total VTE) and low power within individual studies
- For the integrated analysis, only one primary endpoint: composite endpoint of symptomatic VTE or death.
- Pre-specified primary statistical analysis
- No adjustment of type I error was needed

Time to Event Analyses of Multiple TE Bleeds Pooled RECORD 1-4 Safety Population (Question 2c i)

	Riva	Enox	Abs Diff %	Hazard Ratio	
	(N=6183)	(N=6200)	Riva-Enox	Riva vs. Enox	p-Value
	K (%)	K (%)		(95% CI)	
TE Major bleeds					
FDA					0.05
Bayer/J&J				1.84 (0.94,3.62)	0.076
Only One	24 (0.39)	13 (0.21)	0.18		
> One	0 (0.00)	0 (0.00)	0.00		
TE Major bleeding including surgical site					
FDA					0.05
Bayer/J&J				1.35 (1.02,1.79)	0.036
Any	111 (1.80)	85 (1.37)	0.43		
Only One	107 (1.73)	85 (1.37)	0.36		
> One	4 (0.06)	0 (0.00)	0.06		
TE Major or non-major clinically relevant bleeds					
FDA					0.02
Bayer/J&J				1.21 (0.98,1.49)	0.083
Any	197 (3.19)	158 (2.55)	0.64		
Only One	191 (3.09)	151 (2.44)	0.65		
> One	6 (0.10)	7 (0.11)	-0.02		

Other differences (Question 2a)
New requests (Question 2b)

- ?

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/s/

Marcus Cato

4/30/2009 03:23:33 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on April 21, 2009. The purpose of the meeting was to provide clarification regarding the April 17, 2009, chemistry, manufacturing and controls (CMC) information request.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: April 21, 2009
TIME: 10:00 AM - 10:30 AM EST
LOCATION: CDER WO 3560 conf Rm, Bldg21
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Type C, Guidance, CMC

MEETING CHAIR: Dr. Sarah Pope

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF PHARMACEUTICAL SCIENCE / OFFICE OF NEW DRUG QUALITY ASSESSMENT/ DIVISION OF PRE-MARKETING ASSESSMENT AND MANUFACTURING SCIENCE BRANCH V

Patrick Marroum, Ph.D., Quality Reviewer
Sarah Pope, Ph.D., Branch Chief

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 3

Tapash Ghosh, Ph.D., Clinical Pharmacology Reviewer

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/ DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Marcus Cato, M.B.A., Regulatory Health Project Manager

EXTERNAL ATTENDEES:

JOHNSON & JOHNSON

Nancy Micalizzi, J&J CMC RA
Donald Doyle, J&J CMC
Sanjay Jalota, J&J RA
Andrea Kollath, J&J RA

BAYER

Larry Winick, Bayer RA
Robert Kelly, Bayer CMC RA
Stephan Bartel, Bayer CMC RA
Kerstin Pauli, Bayer

BACKGROUND:

On April 17, 2009, FDA sent Johnson and Johnson Pharmaceutical Research and Development (J&J) a CMC information request. The sponsor and FDA agreed to meet to allow for clarification and discuss this request in greater detail.

MEETING OBJECTIVES:

To clarify the April 17, 2009 information request and discuss in greater detail.

DISCUSSION POINTS:

FDA acknowledged that the information requested could be located in the sponsor submitted drug master files (DMFs) however the agency is requesting that J&J submit the information to the NDA. FDA clarified that it was requesting all dissolution profile data along with whatever the sponsor believes necessary to support the dissolution method selection. FDA would not require electronic data sets and the information does not necessary have to be included in module 3 of the application. FDA also requested any available information regarding f2 and data used to calculate and validate f2.

DECISIONS (AGREEMENTS) REACHED:

- J&J would submit the information to the NDA.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- N/A

ACTION ITEMS:

- J&J to submit the information to the NDA

ATTACHMENTS/HANDOUTS:

- None

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/s/

Marcus Cato

4/30/2009 03:13:36 PM

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE:	April 17, 2009
APPLICATION NUMBER:	NDA 22-406

BETWEEN:

Name:	Andrea F. Kollath, DVM Director, Regulatory Affairs
e-mail:	AKollath@its.jnj.com
Representing:	Johnson and Johnson Pharmaceutical Research and Development

AND

Name:	Marcus Cato, M.B.A., Regulatory Project Manager Division of Medical Imaging and Hematology Products HFD-160

SUBJECT:	CMC information

Cato, Marcus

From: Cato, Marcus
Sent: Friday, April 17, 2009 4:03 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Importance: High

Dear Andrea,

We request that you submit the following CMC information on or before April 24, 2009.

Provide the following information in the original NDA submission:

- Full development (justifying the choice of method parameters and discriminatory power) and a validation report for the in-vitro dissolution method.
- Full validation of the analytical method.
- The full in-vitro dissolution data set (preferably in electronic format) used to generate the in-vitro dissolution profiles.
- A full report of the calculations involved (f2 etc.) with generating the proposed specification.

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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/s/

Marcus Cato
4/30/2009 04:59:37 PM
CSO

MEMORANDUM OF E-MAIL CORRESPONDENCE

DATE:	April 16, 2009
APPLICATION NUMBER:	NDA 22-406

BETWEEN:

Name:	Andrea F. Kollath, DVM, Director, Regulatory Affairs
e-mail:	AKollath@its.jnj.com
Representing:	Johnson and Johnson Pharmaceutical Research and Development

AND

Name:	Marcus Cato, M.B.A., Regulatory Project Manager Division of Medical Imaging and Hematology Products HFD-160

SUBJECT:	30 count HDPE bottle marketing

Cato, Marcus

From: Kollath, Andrea [PRDUS] [AKollath@its.jnj.com]
Sent: Thursday, April 16, 2009 5:20 PM
To: Cato, Marcus
Cc: Jalota, Sanjay [PRDUS]
Subject: RE: NDA 22-406
Attachments: emfalert.txt

Hi Marcus

No, we will not withdraw the 30 count HDPE bottle from the application because the 30 count bottle will be used for the SNF/TLC setting.
We will be filing an amendment to the Gurabo Drug product DMF 21592 for the marketed blister packs. (the blister included in the original DMF was a (b) (4) blister)
In the retail setting we will only be marketing a trade blister, with specific packs which would be used as a means to limit off label use for the product.

If you have any questions please let me know.

Kind regards

Andrea

-----Original Message-----
From: Cato, Marcus [mailto:Marcus.Cato@fda.hhs.gov]
Sent: Thursday, April 16, 2009 5:12 PM
To: Kollath, Andrea [PRDUS]
Subject: FW: NDA 22-406

Hi Andrea,

I just remembered to ask about the below e-mail.

Thanks

~Marcus

From: Cato, Marcus
Sent: Thursday, April 09, 2009 9:02 AM
To: 'Jalota, Sanjay [PRDUS]'

Cc: Kollath, Andrea [PRDUS]
Subject: NDA 22-406

Dear Sanjay,

Do you all plan to withdraw the HDPE bottle and market in blister packs? If so, please provide (to the application) written confirmation that you will not be marketing the bottle presentation of rivaroxaban.

Kindly,

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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/s/

Marcus Cato

4/17/2009 03:26:01 PM

CSO

MEMORANDUM OF TELEPHONE CONVERSATION

DATE:	April 16, 2009
APPLICATION NUMBER:	NDA 22-406

BETWEEN:

Name:	Andrea F. Kollath, DVM, Director, Regulatory Affairs
Representing:	Johnson and Johnson Pharmaceutical Research and Development

AND

Name:	Marcus Cato, M.B.A., Regulatory Project Manager Division of Medical Imaging and Hematology Products HFD-160
SUBJECT:	NDA 22-406 application questions

Dr. Kollath.

Called to discuss a number of questions she had outlined in an e-mail. We discuss the question and I responded as outlined below.

1 Stats Meeting April 24th- Have you received any feedback on the stats questions we had sent? Who will be attending this meeting from FDA? Is Dr. Rieves attending?

FDA response: There is no Update at this time our team plans to address all questions in the April 24th Meeting.

2. Peds meeting April 28th- Will there be PERC members attending or not?

FDA response: The PeRC is a congressionally mandated committee with required members. It does not meet with industry.

3. Clin PK feedback- any updates from the reviewers?

FDA response: There is no Update at this time.

4. Trade name status? Have you been able to obtain any feedback?

FDA response: There is no Update at this time

5. I need to request a meeting date for " Major Surgery" indication for sometime in June. I'm sure this will be hard to schedule but we are looking for potentially June 15, 16, or19th.

FDA response: We will review the Meeting Request internally and if Granted we will work to schedule a mutually agreeable date.

6. Safety Surveillance Plan: Do we need to submit an updated SSP ? Any feedback from OSE/Division on next steps?

FDA response: I will follow up with the team and get back to you.

7. You may have already sent me this but who were the attendees at the April 1st Telecon?

FDA response: I will look into it and get back to you.

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/s/

Marcus Cato
4/17/2009 03:14:43 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on April 1, 2009. The purpose of the meeting was to discuss the FDA perspective on the dose and exposure response relationship in certain populations.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: April 1, 2009
TIME: 11:30 AM - 12:30 PM EST
LOCATION: CDER WO 2327 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Type C, Guidance, Clinical Pharmacology

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., Clinical Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/
DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer
Ping Zhao, Ph.D., Clinical Pharmacology Reviewer
Nam Atiqur Rahman, Ph.D., Director

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/
PHARMACOMETRICS DIVISION

Christoffer Tornoe, Ph.D., Clinical Pharmacology Reviewer

EXTERNAL ATTENDEES:

JOHNSON & JOHNSON

Peter DiBattiste, M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters, MD Franchise Medical Leader
Mehul Desai MD, Clinical

Leonard Oppenheimer, PhD. Statistical Sciences
Donald L. Heald, Ph.D., Global Head of Clinical PK
Achiel Van Peer, Ph.D. Global Senior Scientific Leader Clinical Pharmacology
An Thyssen, PhD, Clinpharm Leader Rivaroxaban
An M. Vermeulen PhD Senior Director Advanced PK/PD Modeling & Simulation
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory Lead
Andrea Kollath, DVM, Regulatory Affairs,

BAYER

Scott D. Berkowitz, MD, FACP, FACC, VP, Head, Thrombosis and Hemostasis CV and Coagulation
Andrea Derix, PhD, Sen. Global Regulatory Strategist
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology
Dagmar Kubitza, PhD Global Clinical Pharmacology Project Leader, BSP
Wolfgang M. Mueck, Dr. rer. nat. Director Clinical Pharmacokinetics

BACKGROUND:

On February 5, 2009, FDA sent Johnson and Johnson Pharmaceutical Research and Development (J&J) a Clinical Pharmacology discipline review letter requesting that the sponsor develop a lower strength or scored 10 mg tablet in order to match exposure in patients with renal and/or hepatic dysfunction. Whether or not a lower dose should be available to patients with renal and/or hepatic dysfunction was discussed at the March 19, 2009 Advisory Committee (AC) meeting. The sponsor and FDA agreed to meet to discuss the dose and exposure response relationship in certain populations in greater detail. On March 31, 2009, J&J submitted background information (see attached).

MEETING OBJECTIVES:

To discuss the dose and exposure response relationship in certain populations in greater detail.

DISCUSSION POINTS:

J&J presented the slides submitted March 31, 2009.

Slides 2-3

J&J stated it appeared from the FDA AC presentations that FDA regarded a two-fold increase in exposure as clinically relevant. FDA emphasized that to draw a line in the sand at a particular exposure is not a favorable approach and it is advisable to examine each population. FDA does not agree that a two-fold or greater increase in exposure is the level for clinical relevance. FDA further emphasized that the two-fold exposure increase would be the calculated mean. If the sponsor selected 2.0 as the level for clinical relevance, in a patient population with a mean of 1.8

there would be patients with a two-fold or greater increases in exposure. J&J inquired if FDA considered a two-fold increase in exposure problematic. FDA agreed that a two-fold increase was a problem however it is uncertain of if exposure increases less than two-fold higher than normal are problematic as well. FDA stated its goal would be to match exposure.

FDA maintains its position regarding dose titration, however, it is planning to take action based on the 10 mg dose of rivaroxaban. FDA's view of the labeling will reflect the 10 mg use and as a consequence rivaroxaban would not be recommended in certain populations.

J&J and FDA discussed slides 4-12. FDA informed the sponsor that it is still considering all the information submitted to the application, how the drug will be used in practice and having internal discussions. The Sponsor and FDA agreed to continue discussions at a later date.

DECISIONS (AGREEMENTS) REACHED:

- FDA is planning to take action based on the 10 mg dose of rivaroxaban.
- The Sponsor and FDA agreed to continue discussions at a later date.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- N/A

ACTION ITEMS:

- FDA and J&J to continue discussions at a later date.

ATTACHMENTS/HANDOUTS:

- J&J submitted background information

Rivaroxaban (JNJ-39039039, BAY 59-7939)
10mg Immediate Release Tablets
NDA 22-406

Meeting Date: April 01, 2009

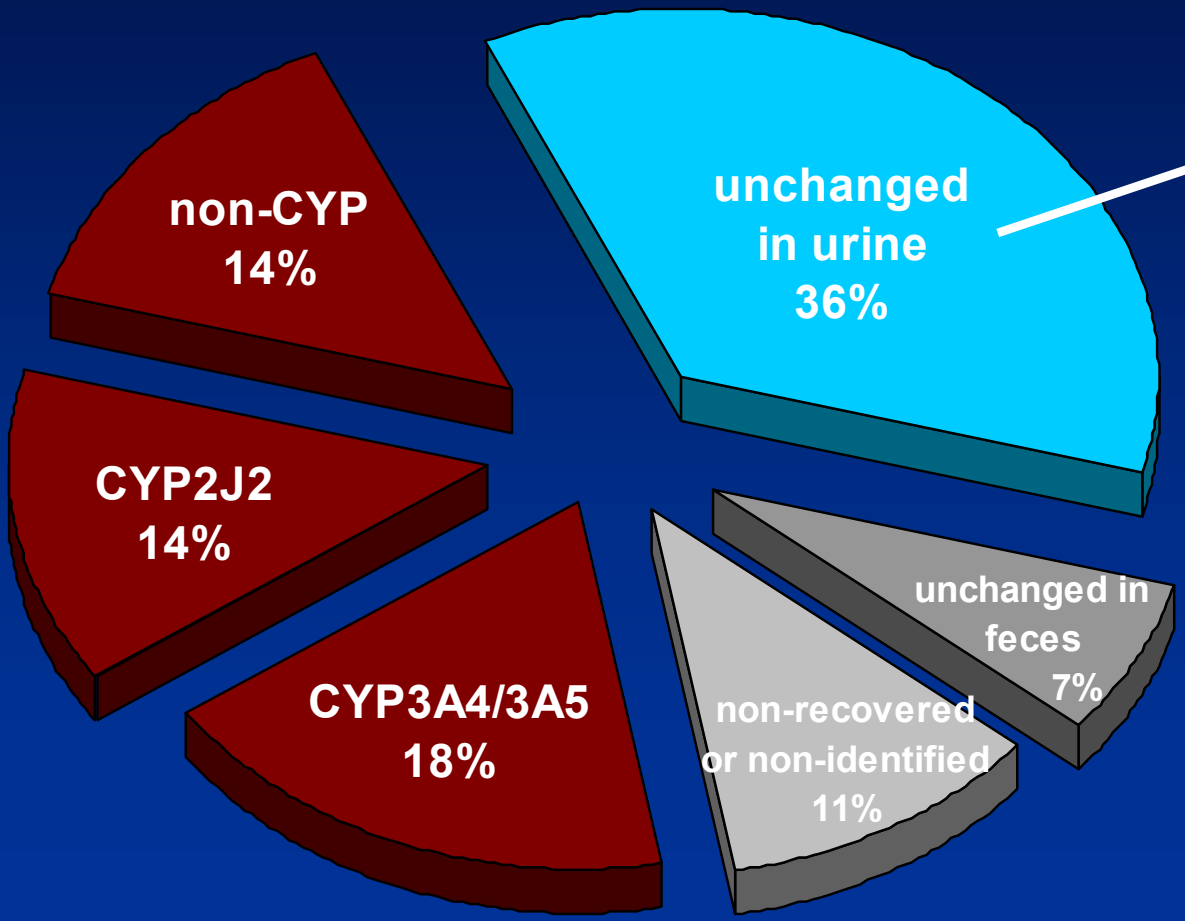
Key Questions (as defined by FDA)

- Is there evidence of dose-exposure-response for efficacy and safety?
  - Shallow dose-response for efficacy
  - Increased major bleeding risk with increasing rivaroxaban dose/exposure
- **Which special populations are at risk for clinically relevant increases in exposure?**
  - Moderate-severe hepatic patients
  - Use of strong CYP3A4/Pgp inhibitors
  - Mild-moderate renal impairment + moderate CYP3A4/Pgp inhibitors
- What are the strategies to address increased exposure and risk of bleeding in special populations ?

Bleeding Dose Response - Sponsor's View

- Dose and exposure response relationships similar
- 30-50% increase in bleeding events with rivaroxaban dose increase from 10 mg to 20 mg
- Limit exposures above 2X increase

Multiple Elimination Pathways



30% active renal secretion (Pgp/Bcrp)

6% glomerular filtration

Hepatic Impairment

Moderate hepatic impairment (Child Pugh B):

- **Pronounced effect on <u>both</u> PK and PD**
- **Prolonged PT at baseline (approx. 3 seconds) → underlying coagulopathy → inherent bleeding risk**
- **Increased slope for PT/rivaroxaban plasma concentration relationship by more than 2-fold: 3.1 seconds/(100 µg/L) for healthy subjects vs 7.8 seconds/(100 µg/L) for Child Pugh Grade B patients) → reflects underlying disease**

Severe hepatic impairment (Child Pugh C): not studied

Table 3-10: Effect of Hepatic Impairment - Mean Ratios (Stratum 2/Stratum 1) of Pharmacokinetic and Pharmacodynamic Parameters and Associated 90% Confidence Intervals (Phase 1)

Stratum 1	Stratum 2	AUC	Cmax or E_{max}
PK parameters AUC and Cmax			
Normal Hepatic Function	Child-Pugh A	1.15 (0.85 - 1.57)	0.97 (0.75 - 1.25)
	Child-Pugh B	2.27 (1.68 - 3.07)	1.27 (0.99 - 1.63)
Percent Inhibition of FXa activity			
Normal Hepatic Function	Child-Pugh A	1.08 (0.70 - 1.68)	0.98 (0.86 - 1.13)
	Child-Pugh B	2.59 (1.69 - 3.98)	1.24 (1.09 - 1.42)
Relative Prolongation of PT			
Normal Hepatic Function	Child-Pugh A	1.06 (0.79 - 1.42)	1.02 (0.93 - 1.12)
	Child-Pugh B	2.14 (1.61 - 2.84)	1.41 (1.28 - 1.54)

n=8/Child-Pugh class; n=16 for subjects with normal hepatic function

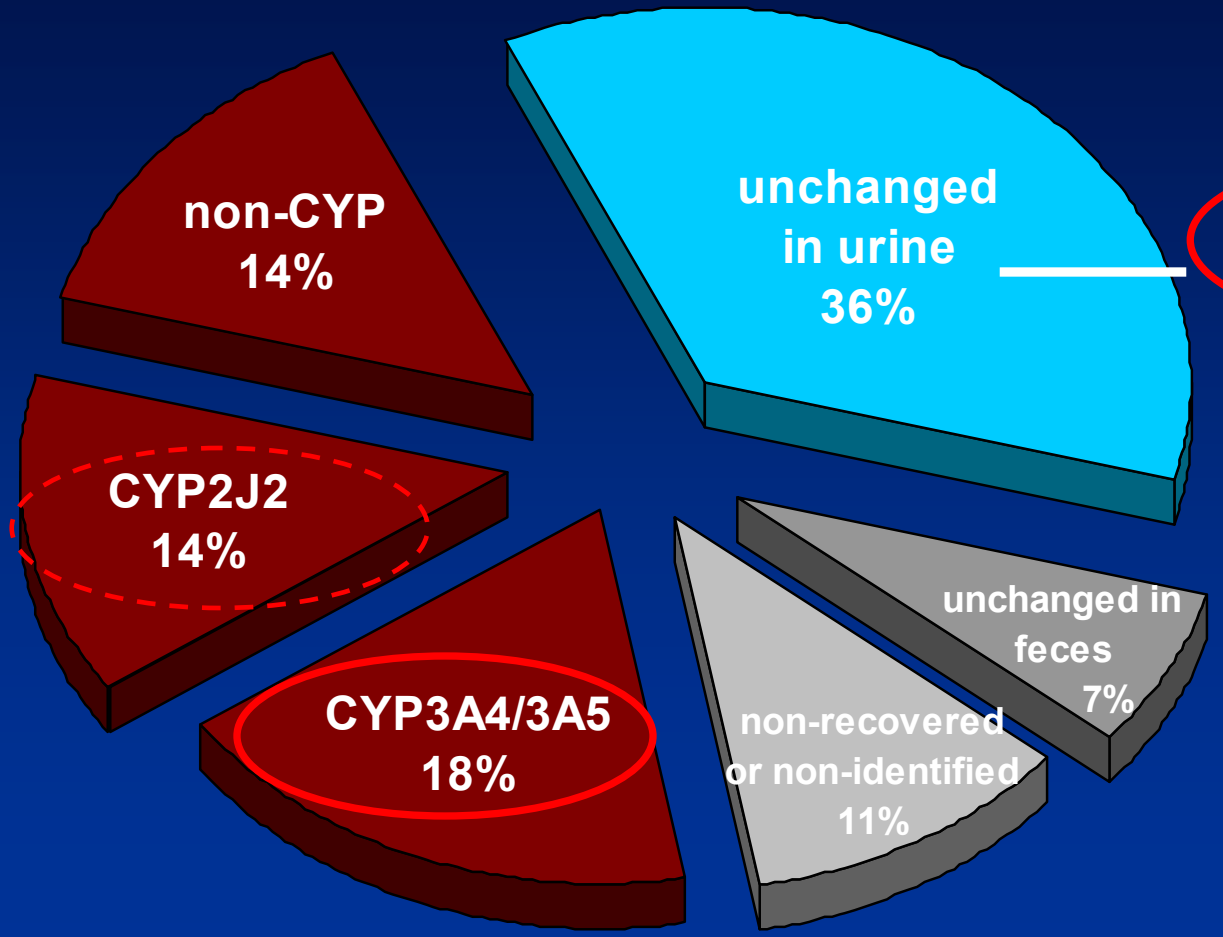
Hepatic Impairment - Sponsor's View

- Intent is to contraindicate hepatic disease with any prolongation of PT
  - Not many of these patients have elective joint replacement surgery
  - Broader than just moderate or severe Child –Pugh score
  - Increased risk for bleeding even with a lower dose due to underlying liver disease and increased PD sensitivity

Pharmacokinetic Interactions
CYP3A4/Pgp Inhibitors

Influence of		AUC ratio [90%CI]		C_{max} ratio [90%CI]	
Strong inhibitor of both CYP 3A4 and P-gp					
ketoconazole	200 mg qd	1.82	[1.59 - 2.08]	1.53	[1.27 - 1.85]
ketoconazole	400 mg qd	2.58	[2.36 - 2.82]	1.72	[1.61 - 1.83]
ritonavir	600 mg bid	2.53	[2.34 - 2.74]	1.55	[1.41 - 1.69]
Strong CYP3A4 inhibitor & weak-to-moderate P-gp inhibitor					
clarithromycin	500 mg bid	1.54	[1.44 – 1.64]	1.40	[1.30 - 1.52]
Moderate CYP 3A4 & P-gp inhibitor					
erythromycin	500 mg tid	1.34	[1.23 - 1.46]	1.34	[1.21 - 1.48]

Impact of Renal Impairment and CYP3A4 Inhibition



30% active renal secretion (Pgp/Bcrp)

6% glomerular filtration

max. blockade renal clearance ~ 80%

(severe renal impairment)

max. blockade hepatic clearance ~ 90%

(strong CYP3A4 Pgp inhibitor - ketoconazole)

Phase 1 Estimations: Impact of Renal Impairment and Concomitant Use of CYP3A4 Inhibitor

x-fold Increase in AUC (vs Normal Renal Function)

	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
	> 80 mL/min	50-80 mL/min	30-50 mL/min	<30 mL/min
No CYP3A4 inh	1.00	1.49	1.66	1.79
30% CYP3A4 inh	1.09	1.64	1.84	1.99
50% CYP3A4 inh[a]	1.15	1.75	1.98	2.15
90% CYP3A4 inh[b]	1.32	2.04	2.35	2.57

[a] Erythromycin reflects moderate CYP3A4 inhibitor [b] clarithromycin reflects strong CYP3A4 inhibitor

Ketoconazole & Ritonavir (strong inhibitors of both CYP3A4 and Pgp) increases AUC 2.6/2.5 fold

CYP3A4 clearance: 23% of total clearance

38% of hepatic clearance

Frequency of Combined Renal Impairment and Concomitant Use of CYP3A4 Inhibitor Pooled RECORD 1-4 Safety Population

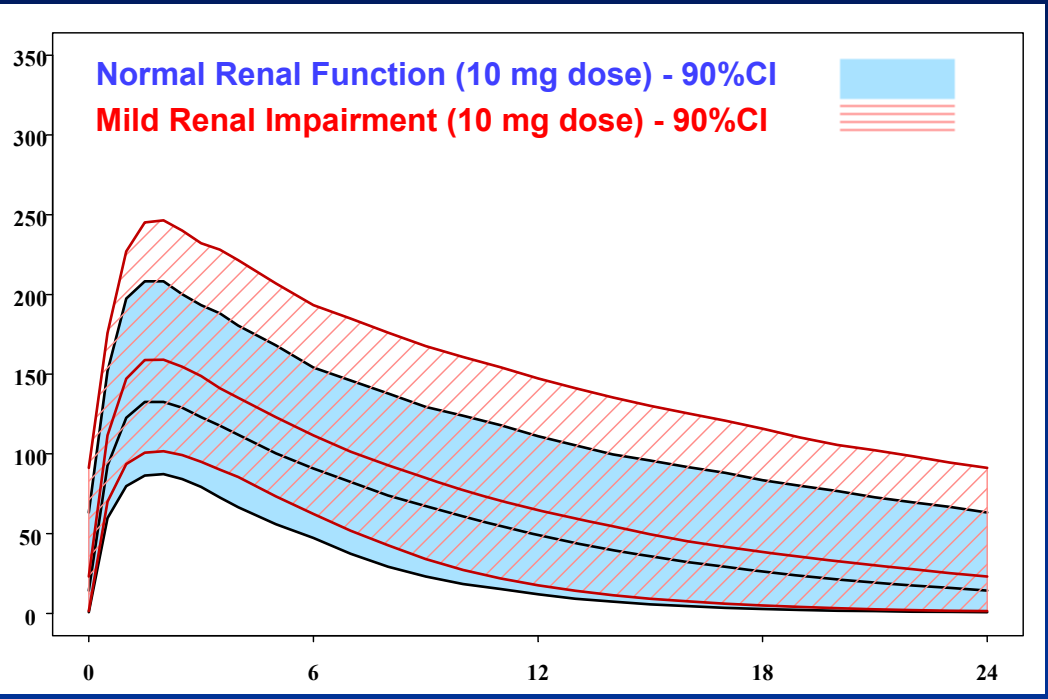
Total N=12268	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
	> 80 mL/min	50-80 mL/min	30-50 mL/min	<30 mL/min
No CYP3A4 inh	54.9% (6739)	31.6% (3878)	5.8% (717)	0.4% (52)
Weak CYP3A4 inh (30%)	1.7% (208)	0.9% (107)	0.2% (20)	<0.1% (1)
Moderate CYP3A4 inh (50%)	2.0% (252)	1.7% (209)	0.4% (50)	<0.1% (4)
Strong CYP3A4 inh (90%)	0.1% (16)	0.1% (13)	<0.1% (2)	<0.1% (0)

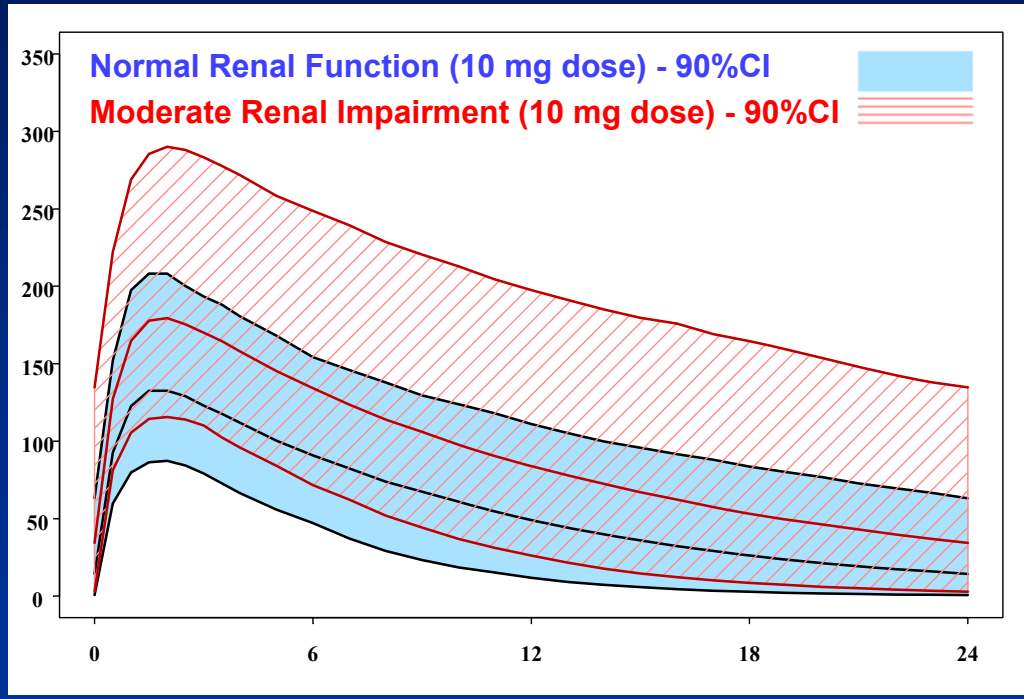
Frequency of Combined Renal Impairment and Concomitant Use of CYP3A4 Inhibitor US Pooled RECORD 1-4 Safety Population

Total N=1709	Normal Renal Function	Mild Renal Impairment	Moderate Renal Impairment	Severe Renal Impairment
	> 80 mL/min	50-80 mL/min	30-50 mL/min	<30 mL/min
No CYP3A4 inh	62.4% (1067)	22.8% (389)	4.7% (80)	0.2% (3)
Weak CYP3A4 inh (30%)	2.0% (35)	0.6% (10)	0.1% (2)	<0.1% (0)
Moderate CYP3A4 inh (50%)	5.0% (86)	1.7% (29)	0.3% (5)	<0.1% (0)
Strong CYP3A4 inh (90%)	0.1% (2)	<0.1% (1)	<0.1% (0)	<0.1% (0)

Predicted Steady State Plasma Concentration Window 10 mg qd in Phase 2 Target Population

Normal Renal Function vs Mild and Moderate Renal Impairment



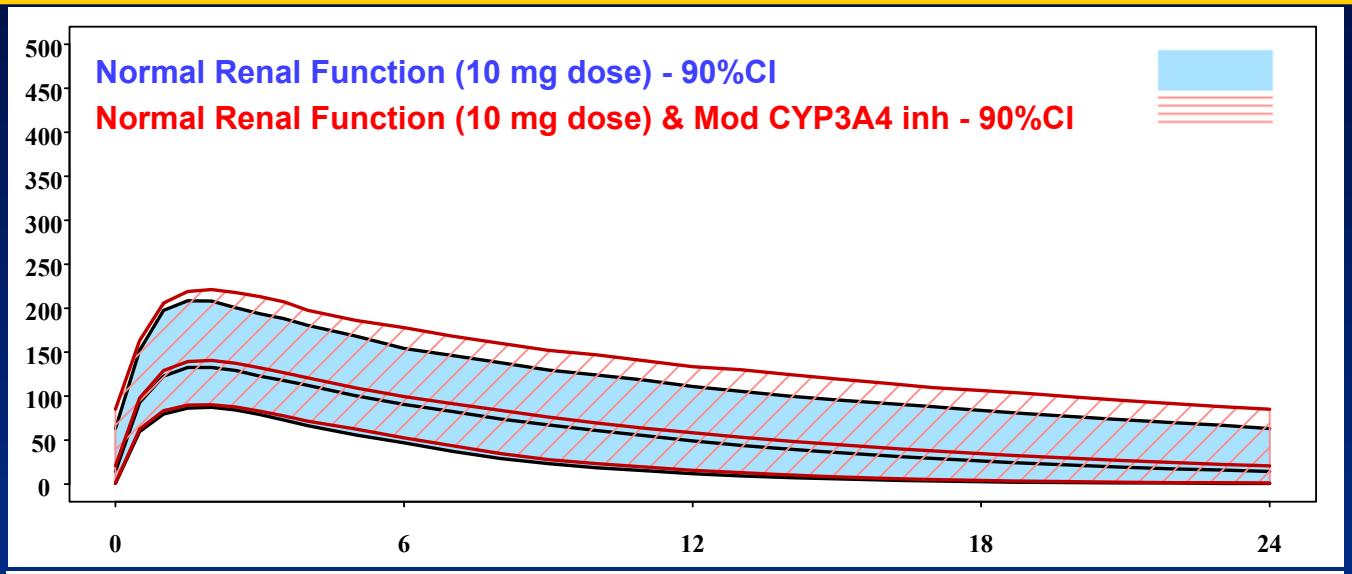


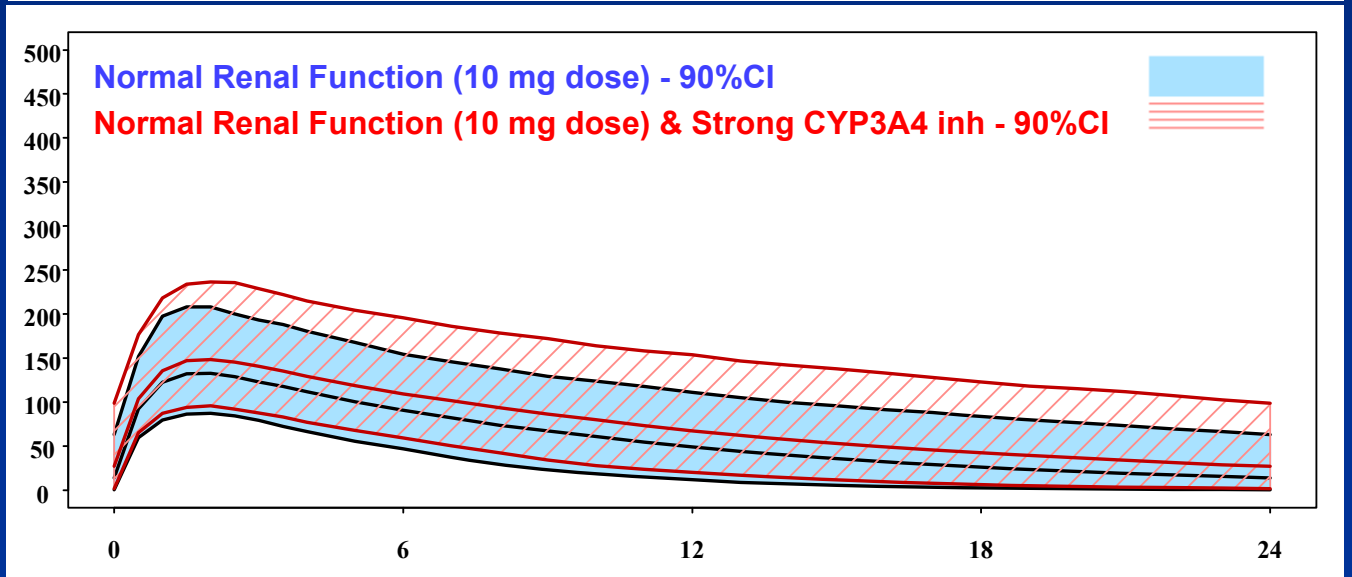
Renal Impairment - Sponsor's View

- All levels of renal impairment (including severe) less than 2x increase in exposures (AUC)
- Sufficient Phase 3 data in moderate renal impairment to support use of 10 mg dose
- Use 10 mg dose with caution in severe renal impairment due to limited data (exclusion due to enoxaparin in Phase 3)
- Use not recommended in renal failure (dialysis)
  - No data
  - Very uncommon to have joint replacement and marked increase in complication rates

Predicted Steady State Plasma Concentration Window 10 mg qd in Phase 2 Target Population

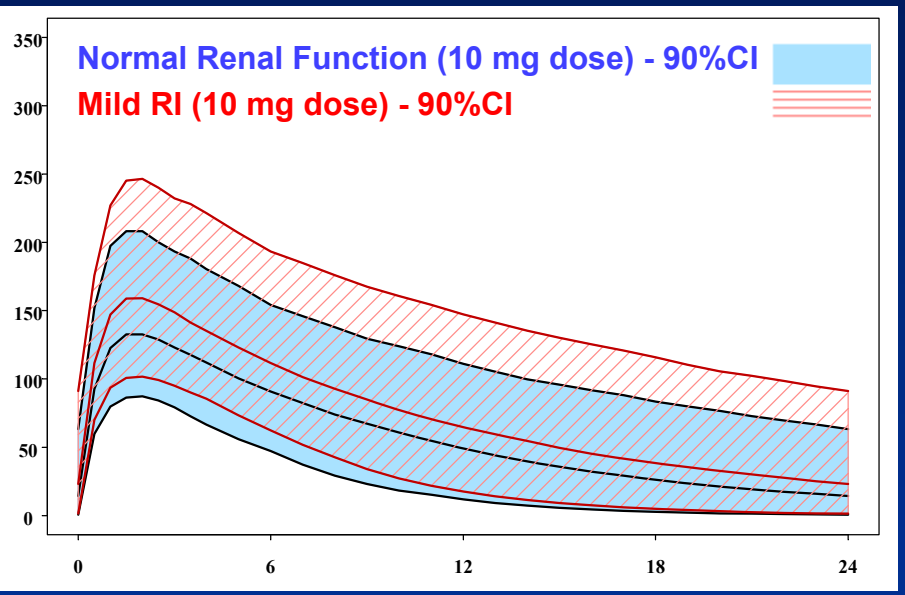
Normal Renal Function and Moderate or Strong CYP 3A4 Inhibition

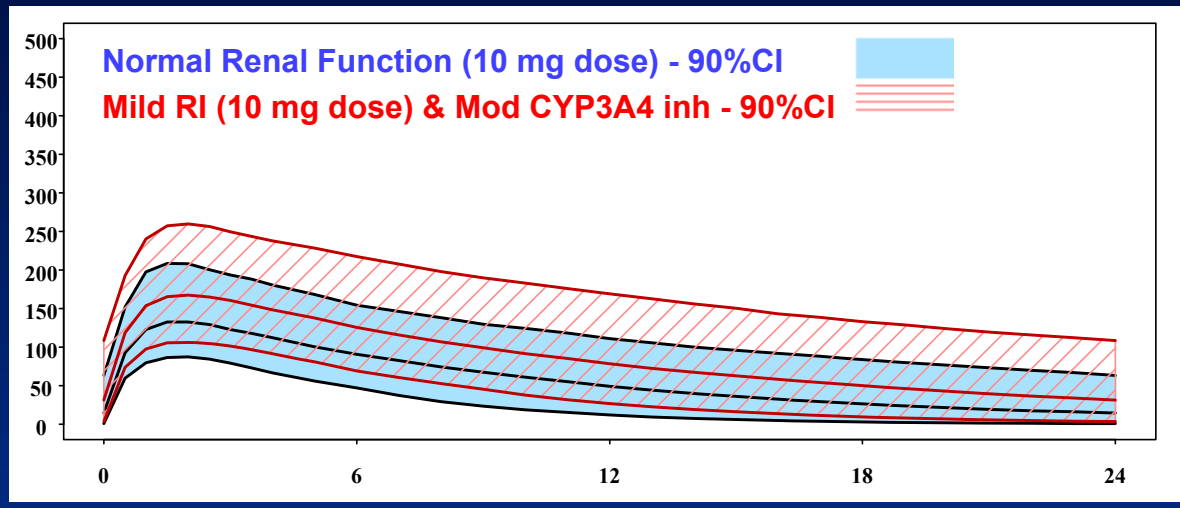


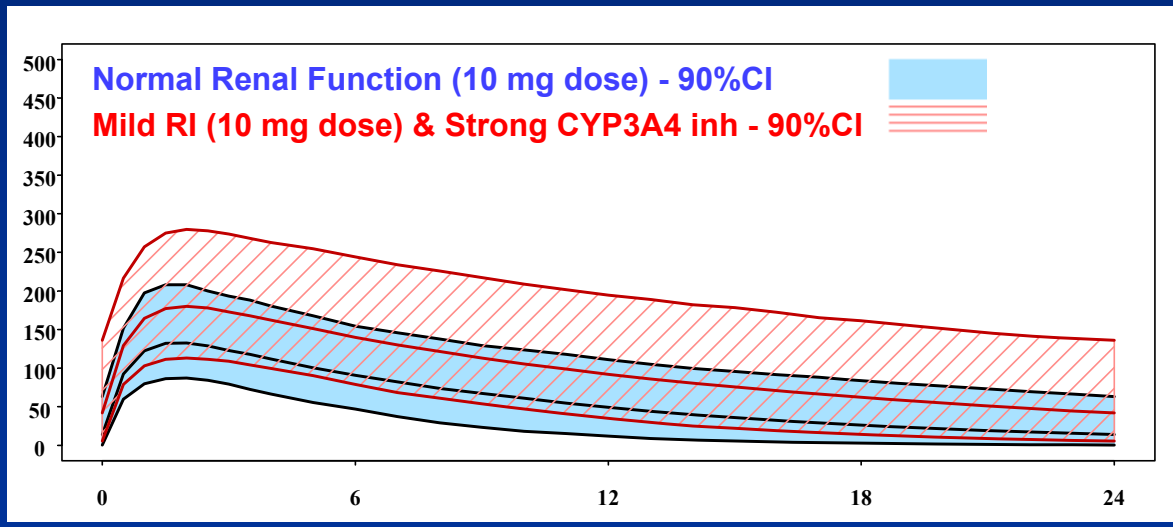


Predicted Steady State Plasma Concentration Window 10 mg qd in Phase 2 Target Population

Mild Renal Impairment and Moderate or Strong CYP 3A4 Inhibition

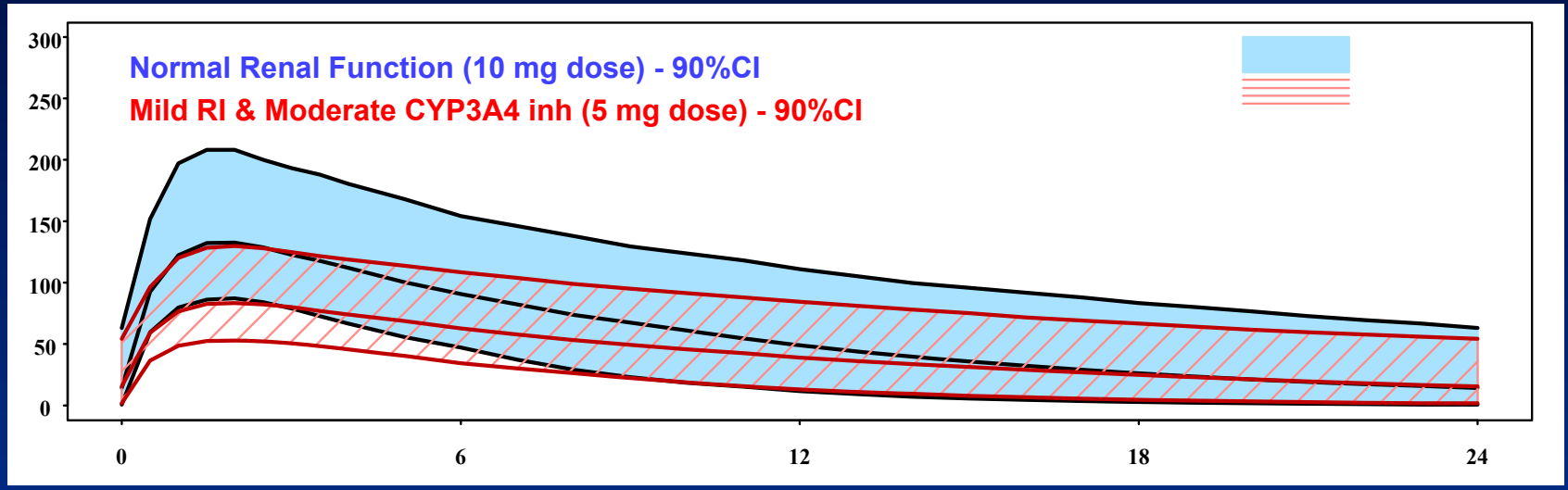


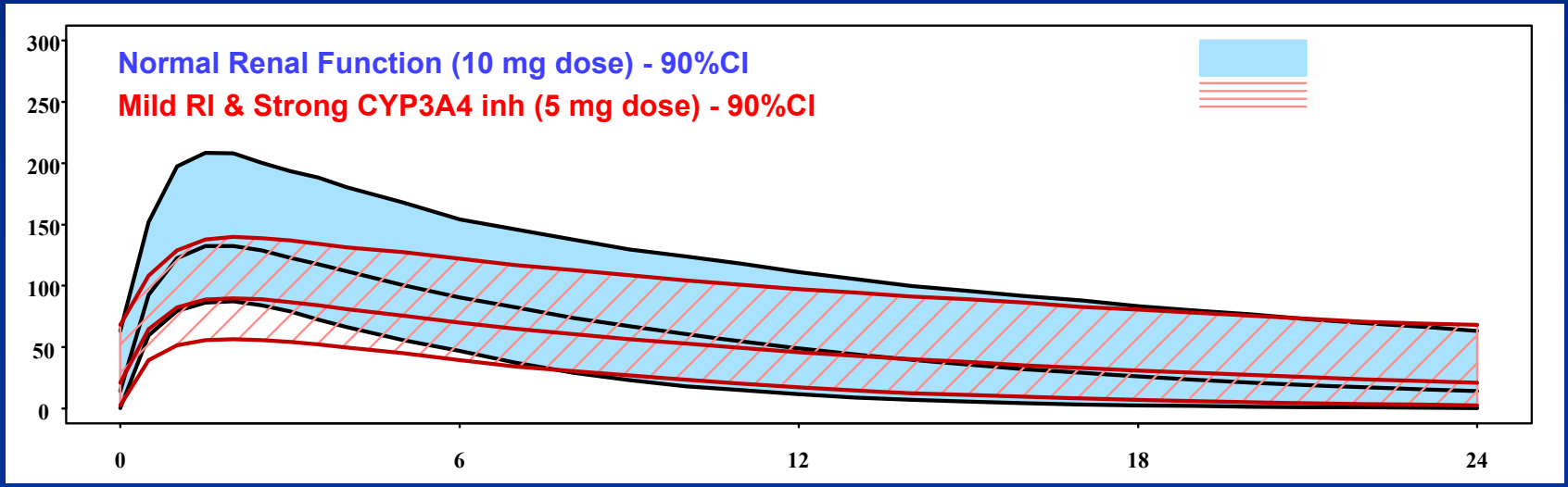




Predicted Steady State Plasma Concentration Window 5 mg qd in Phase 2 Target Population

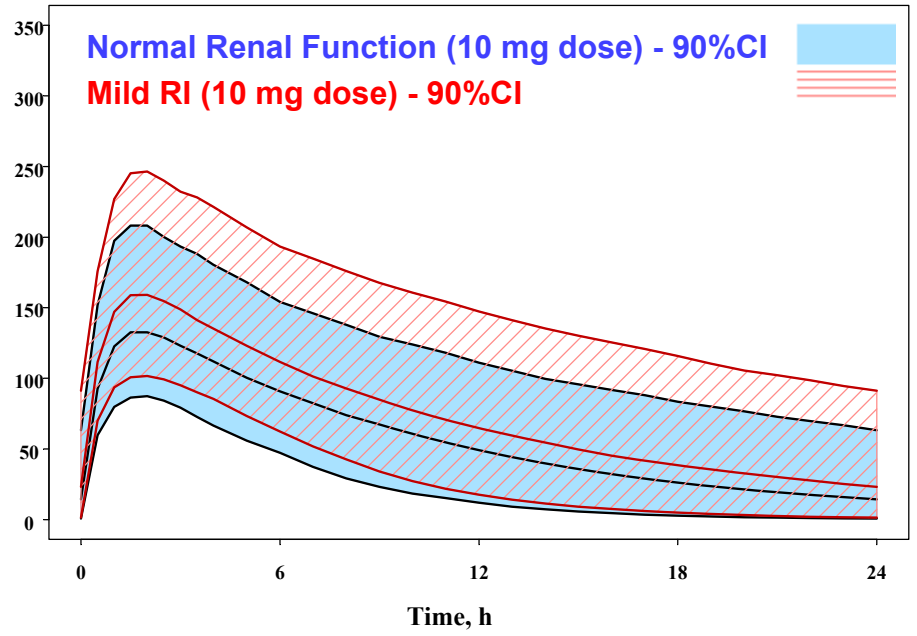
Mild Renal Impairment and Moderate or Strong CYP 3A4 Inhibition

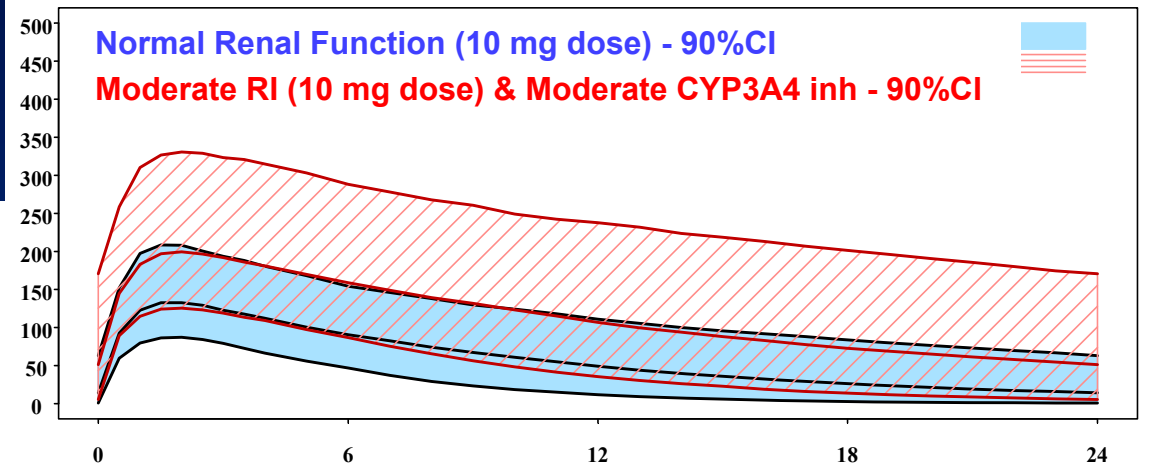


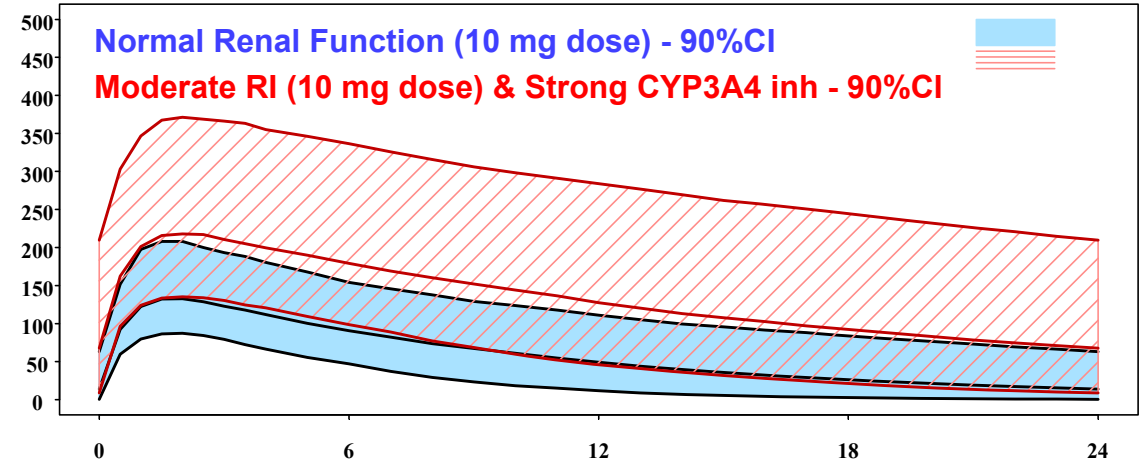


Predicted Steady State Plasma Concentration Window 10 mg qd in Phase 2 Target Population

Moderate Renal Impairment and Moderate or Strong CYP 3A4 Inhibition

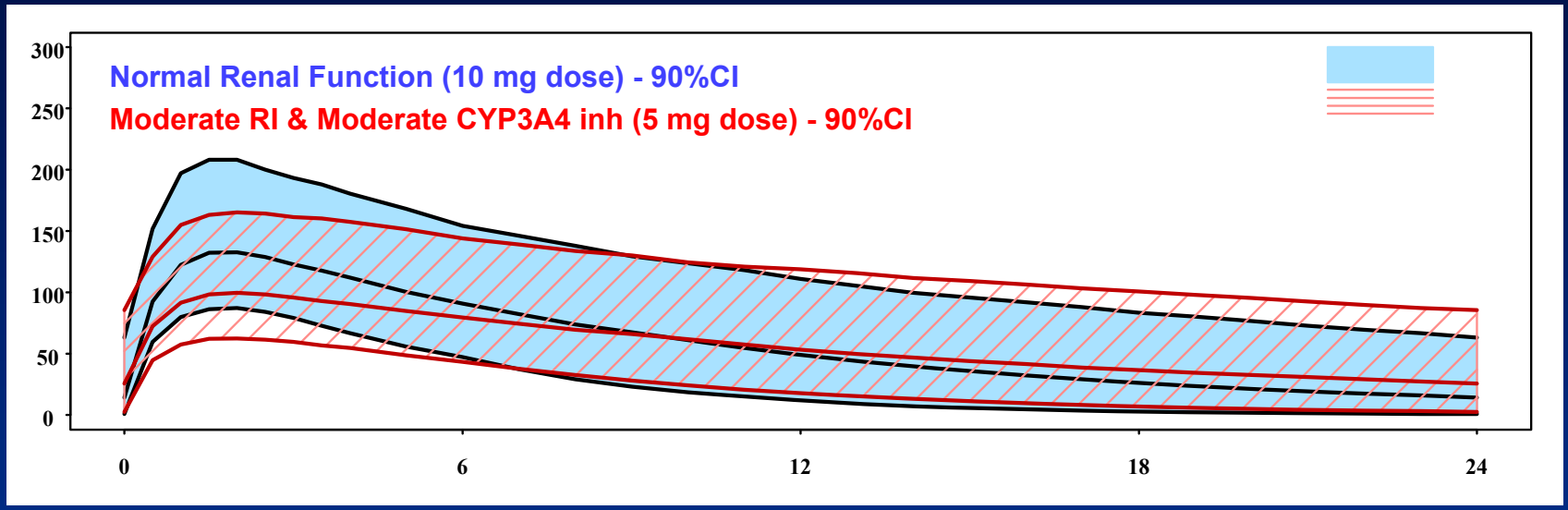


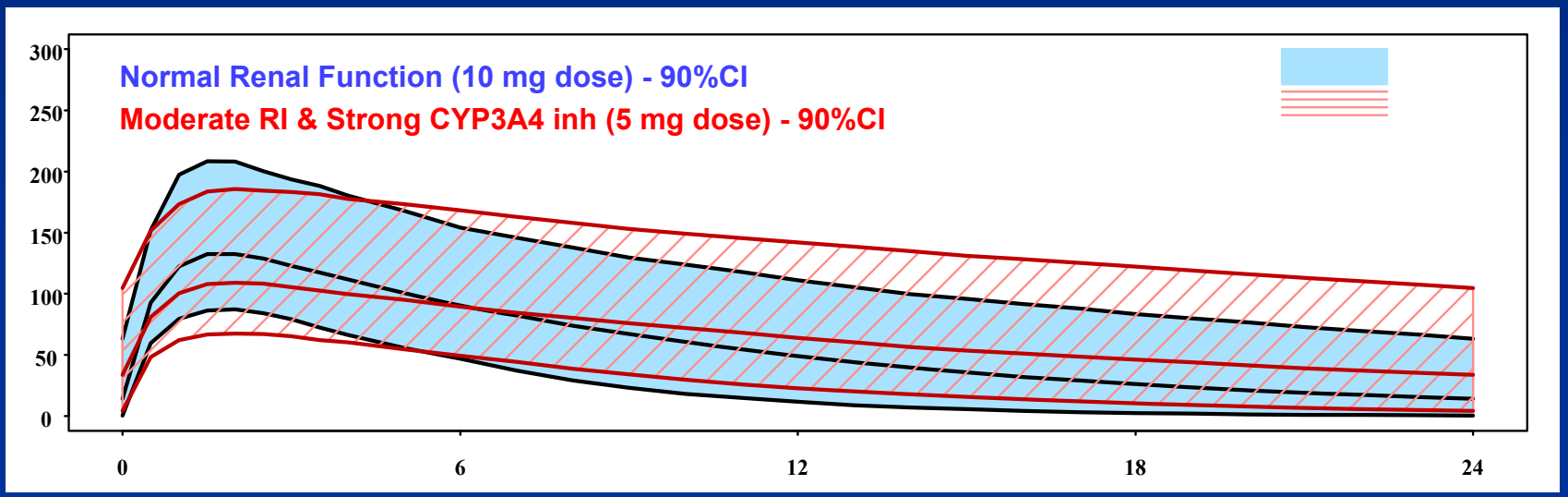




Predicted Steady State Plasma Concentration Window 5 mg qd in Phase 2 Target Population

Moderate Renal Impairment and Moderate or Strong CYP 3A4 Inhibition



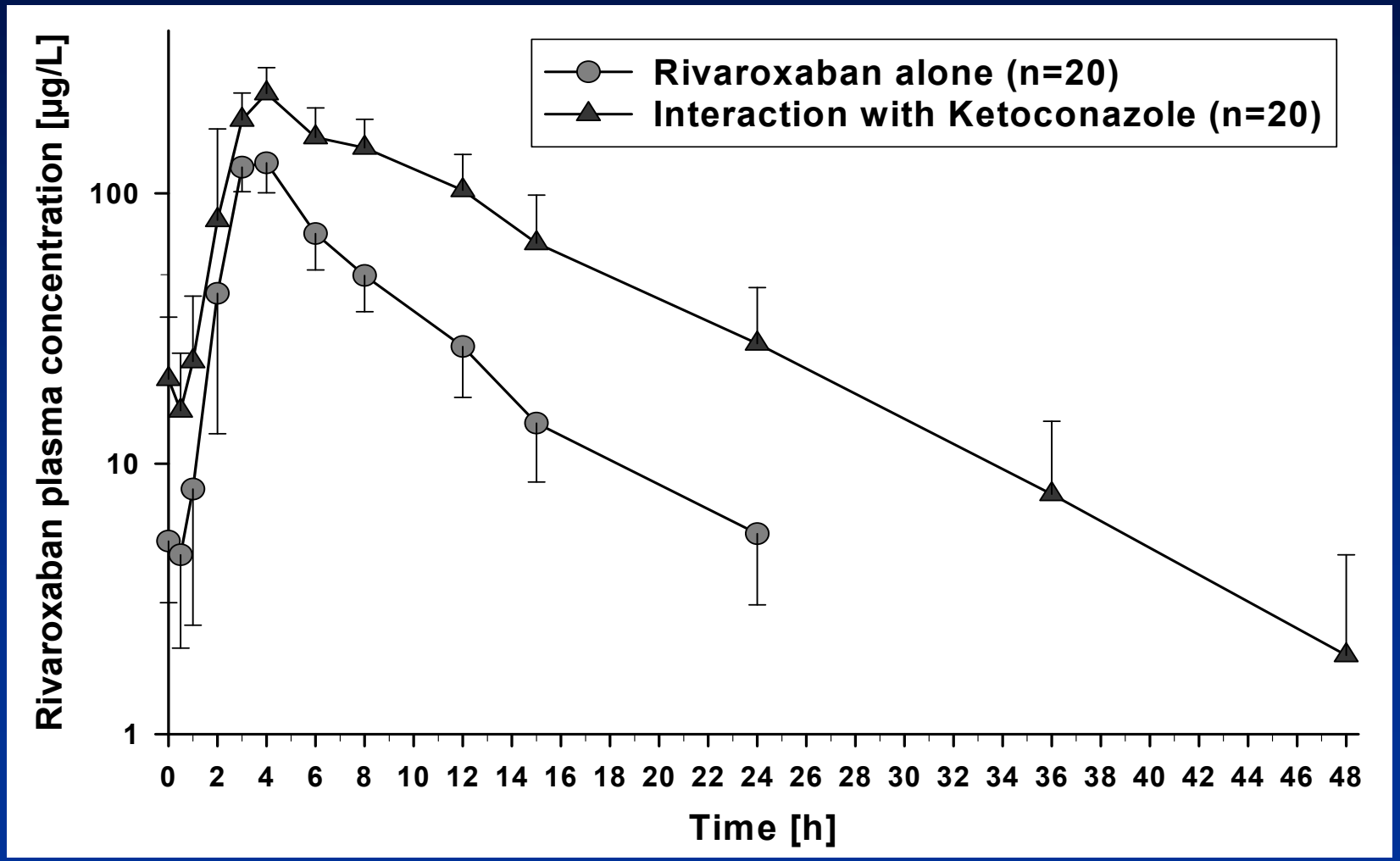


Renal Impairment and CYP Inhibition - Sponsor's View

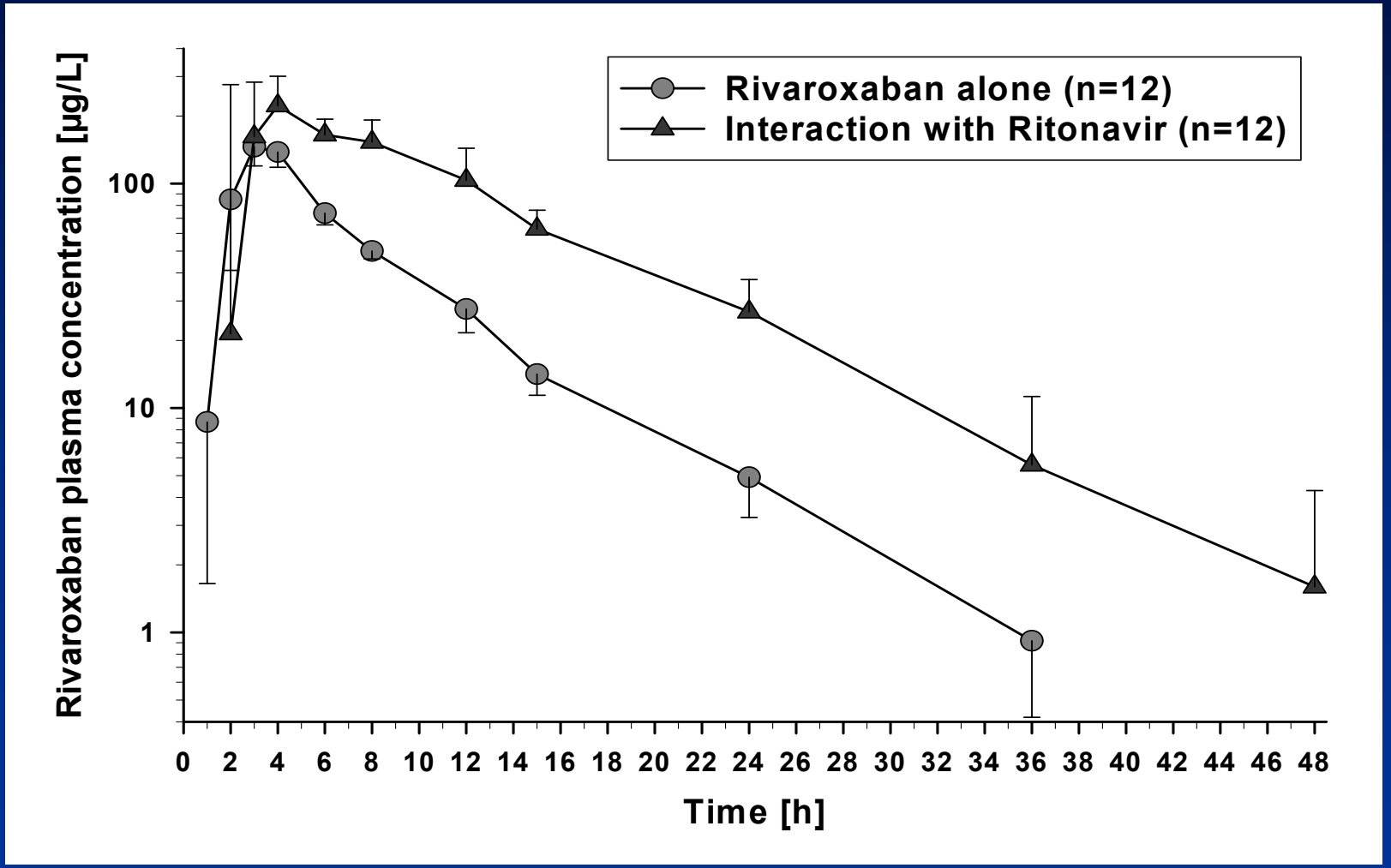
- No special instructions necessary for normal renal function or mild renal impairment + CYP3A4 inhibitor
- Caution for use with moderate CYP inhibition and either moderate or severe renal impairment
  - Exposures about 2x increase
  - Not a common situation
  - Not contraindicated since overall benefit risk may be favourable
- Ketoconazole and ritonavir represent situations with strong inhibition of CYP and severe renal impairment (i.e. lower right quadrant)
  - Use not recommended due to exposures >2x increase
  - Not a common situation
  - Not contraindicated since overall benefit risk may be favourable

Background

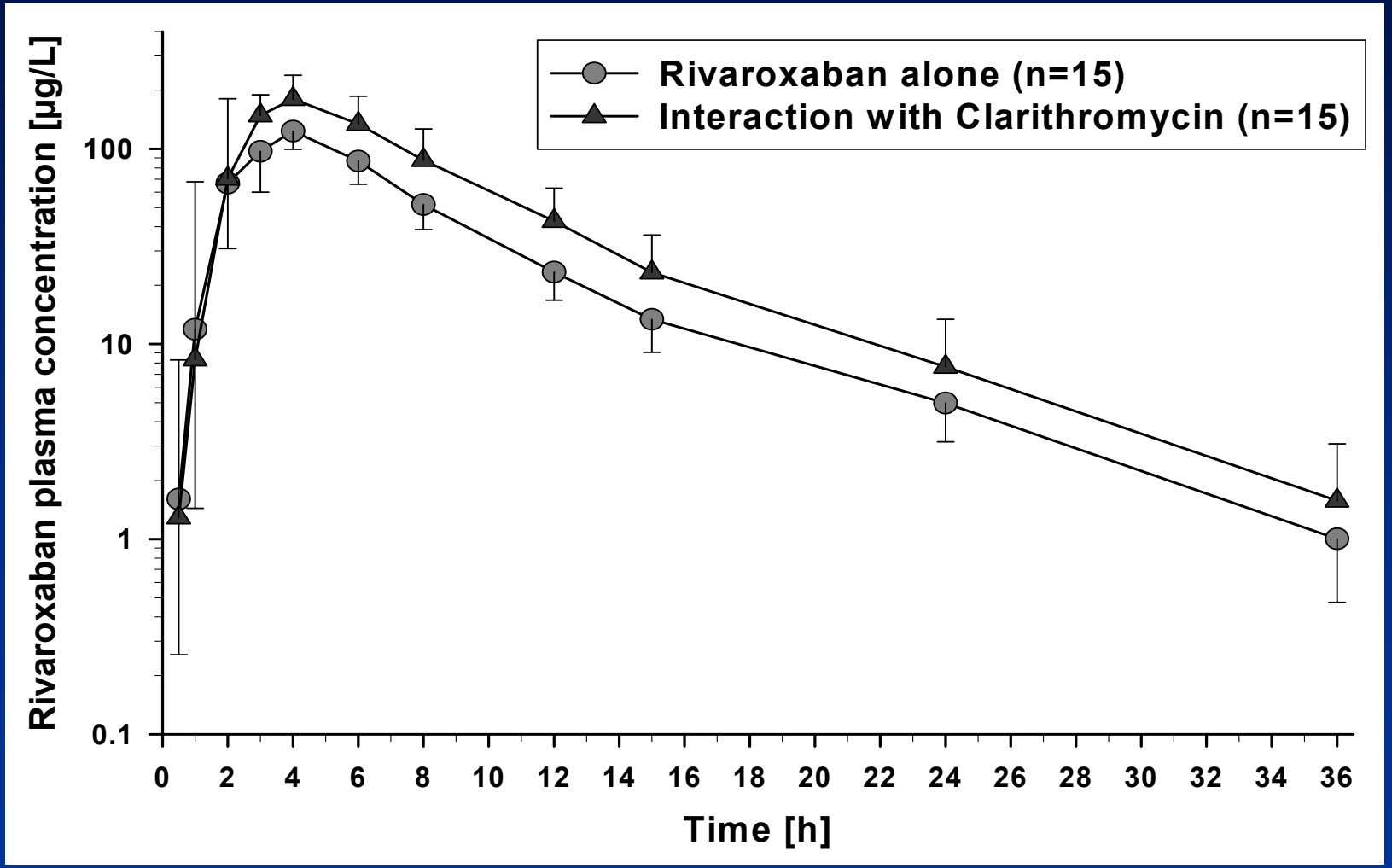
Ketoconazole 400 mg qd - Rivaroxaban 10 mg Interaction
Steady-State Plasma Concentrations of Rivaroxaban



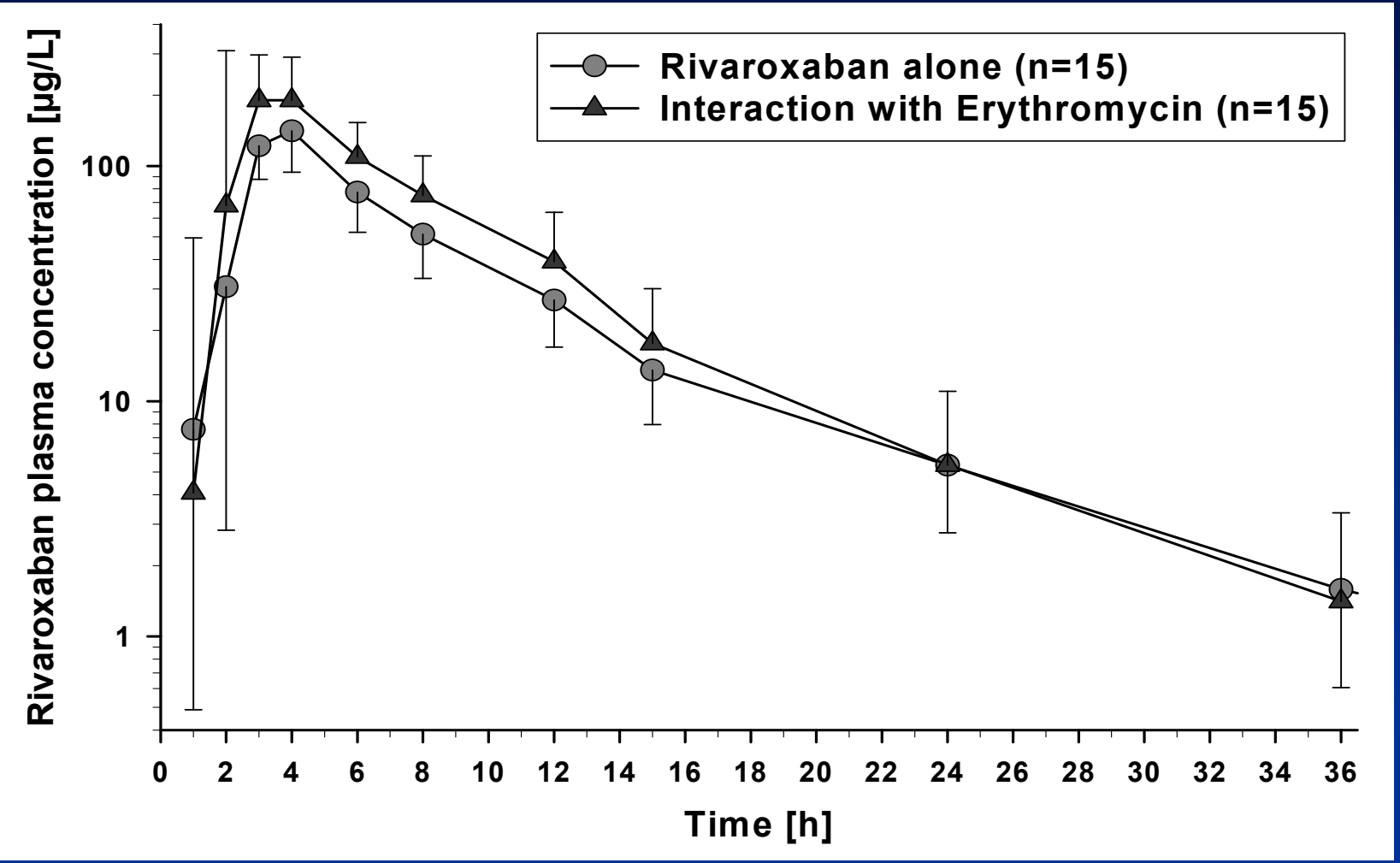
Ritonavir 600 mg bid - Rivaroxaban 10 mg Interaction
Plasma Concentrations of Rivaroxaban



Clarithromycin 500 mg bid - Rivaroxaban 10 mg Interaction
Plasma Concentrations of rivaroxaban



Erythromycin 500 mg tid - Rivaroxaban 10 mg
Interaction Plasma Concentrations of Rivaroxaban



In vivo Effect of Inhibitors of CYP3A4 and Pgp on Plasma Exposure and Clearance

Treatment	Parameter	Estimate (90% CI)
Rivaroxaban + Erythromycin 500 mg tid	AUC	1.34 (1.23 – 1.46)
	C_{max}	1.38 (1.21 – 1.48)
	CL/f	0.75 (0.69 – 0.81)
	CL_{RS}	1.07 (0.90 – 1.27)
Rivaroxaban + Clarithromycin 500 mg bid	AUC	1.54 (1.44 – 1.64)
	C_{max}	1.40 (1.30 – 1.52)
	CL/f	0.65 (0.61 – 0.69)
	CL_{RS}	0.90 (0.80 – 1.01)
Rivaroxaban + Ketoconazole 200 mg od	AUC	1.82 (1.59 – 2.08)
	C_{max}	1.53 (1.27 – 1.85)
	CL/f	0.55 (0.48 – 0.63)
Rvaroxaban + Ketoconazole 400 mg od	AUC	2.58 (2.36 – 2.82)
	C_{max}	1.72 (1.61 – 1.83)
	CL/f	0.39 (0.35 – 0.42)
	CL_{RS}	0.56 (0.47 – 0.68)
Rivaroxaban + Ritonavir 600 mg bid	AUC	2.52 (2.34 – 2.74)
	C_{max}	1.55 (1.41 – 1.69)
	CL/f	0.40 (0.37 – 0.43)
	CL_{RS}	0.18 (0.14 – 0.24)

In Vitro DDI in Human Liver Microsomes - Inhibition of Rivaroxaban Oxidative Metabolism

- 82 compounds at 6 concentrations tested
- Inhibition of M2 formation

  (CYP3A4/3A5 and 2J2 mediated)
- Inhibition of M9 formation

  (CYP3A4/3A5 mediated)
- HIV protease inhibitors and antifungal azoles inhibited both M2 and M9 formation
- Some CYP3A4 substrates inhibited M9 formation more than M2 formation (e.g., erythromycin), some inhibited M2 formation more than M9 formation (e.g., verapamil)

In vitro Inhibition of Oxidative Metabolism and Renal Secretion

Inhibitor	C_{max} [µM]	M-2 form. CYP3A4/ CYP2J2 IC_{50} [µM]	M-9 form. CYP3A4 IC_{50} [µM]	P-gp Transp. IC_{50} [µM]	Bcrp Transp. IC_{50} [µM]	In vivo x-fold increase exposure
Ketoconazole 400 mg qd	10	0.28	0.28	9.0	5.8	AUC: 2.6 C_{max}:1.7
Ritonavir 600 mg bid	15	0.54	0.42	27.9	11.0	AUC: 2.5 C_{max}:1.6
Clarithromycin 500 mg bid	3.1	189	44	- NS at 10	- NS at 10	AUC: 2.5 C_{max}:1.4
Erythromycin 500 mg tid	4.2	>200	37	- NS at 10	- [NS at 10	AUC and C_{max}:1.3

In Vitro DDI - HIV Protease Inhibitors

Inhibitor	Cmax [µM]	M2 form. CYP3A4/ CYP2J2 IC50 [µM]	M9 form. CYP3A4 IC50 [µM]	P-gp transp. IC50 [µM]	Bcrp transp. IC50 [µM]
Ritonavir 600 mg bid	15	0.54	0.42	27.9	11.0
Atazanavir 400 mg od	5.4	2.4	1.2	-	-
Indinavir 800 mg tid	12.9	4.3	1.7	-	-
Saquinavir 1200 mg tid	1.6	11	10	-	-

In Vitro DDI - Azole Antifungals

Inhibitor	Cmax [µM]	M2 form. CYP3A4/ CYP2J2 IC50 [µM]	M9 form. CYP3A4 IC50 [µM]	P-gp transp. IC50 [µM]	Bcrp transp. IC50 [µM]
Ketoconazole 400 mg od	10	0.28	0.28	9.0	5.8
Itraconazole 200 mg bid	2.8	5.6	4.0	0.16	-
Clotrimazole (non-systemic)	< 0.03	10	0.25	13.6	-
Miconazole (non-systemic)	< 0.96	3.6	2.2	15.1	-
Fluconazole 400 mg od	60	179	20	not known	not known

In Vitro DDI – P-gp Inhibitors

Inhibitor	Cmax [µM]	M2 form. CYP3A4/ CYP2J2 IC50 [µM]	M9 form. CYP3A4 IC50 [µM]	P-gp transp. IC50 [µM]	Bcrp transp. IC50 [µM]
Ivermectin 12 mg	0.11	not known	not known	0.25	not known
Cyclosporin 1.8 mg/kg/day	0.88	9.7	3.6	2.3	-
Quinidine	8.9	not known	not known	4.3	not known
Amiodarone 400 mg qd	3.5	> 200	> 200	14.1	not known
Diltiazem 240 mg qd	0.5	84	33	78 (for digoxin)	not known
Verapamil 240 mg qd	0.56	21	52	4.3	-

Summary of Efficacy by CYP3A4 or Pgp Inhibitor Use RECORD 1-4 Pooled Studies

Subgroup	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Odds/Hazard ratio (95%CI)
Total VTE			
CYP or Pgp no	156/3918 (3.98)	356/3942 (9.03)	0.42 (0.34, 0.51)
CYP or Pgp yes	25/330 (7.58)	46/322 (14.29)	0.49 (0.28,0.85)
Major VTE			
CYP or Pgp no	26/4317 (0.60)	109/4330 (2.52)	0.23 (0.15, 0.36)
CYP or Pgp yes	6/360 (1.67)	19/347 (5.48)	0.28 (0.09, 0.75)
Symptomatic VTE/death			
CYP or Pgp no	32/5682 (0.56)	70/5705 (1.23)	0.46 (0.30, 0.69)
CYP or Pgp yes	3/501 (0.60)	12/495 (2.42)	0.24 (0.07, 0.86)

Summary of Bleeding Events by CYP3A4 or Pgp Inhibitor Use RECORD 1-4 Pooled Studies

Subgroup	Rivaroxaban n/N (%)	Enoxaparin n/N (%)	Hazard ratio (95%CI)
Major or non-major clinically relevant bleeding event			
CYP or Pgp no	175/5682 (3.08)	149/5705 (2.61)	1.18 (0.95, 1.46)
CYP or Pgp yes	22/501 (4.39)	9/495 (1.82)	2.37 (1.09, 5.16)
Any bleeding event			
CYP or Pgp no	381/5682 (6.71)	372/5705 (6.52)	1.03 (0.89, 1.18)
CYP or Pgp yes	53/501 (10.58)	29/495 (5.86)	1.81 (1.15, 2.85)

CYP3A4 or Pgp Inhibitors in Phase 3
Pooled Phase 3 - PT Analysis Population

Drug	Rivaroxaban (N=6093)	Drug	Rivaroxaban (N=6093)
Any CYP3A4 or Pgp inhibitors	460		
Amiodarone	47	Fluconazole	9
Aprepitant	6	Fluoxetine	52
Cyclosporin	8	Fluvoxamine	8
Cimetidine	119	Itraconazole	1
Clarithromycin	9	Ketoconazole	3
Diltiazem	101	Quinidine	1
Erythromycin	8	Verapamil	109

weak CYP3A4 inhibitor moderate CYP3A4 inhibitor strong CYP3A4 inhibitor

CYP3A4 Inhibitors in Phase 3
Pooled Phase 3 - PT Analysis Population

Drug	Rivaroxaban (N=6093)	Drug	Rivaroxaban (N=6093)
Any CYP3A4 inhibitors	451	Diltiazem	101
Weak inhibitors		Erythromycin	8
Cimetidine	119	Fluconazole	9
Fluoxetine	52	Verapamil	109
Fluvoxamine	8	Strong inhibitors	
Moderate inhibitors		Clarithromycin	9
Aprepitant	6	Itraconazole	1
Amiodarone	47	Ketoconazole	3

weak inhibitor moderate inhibitor strong inhibitor

Pgp Inhibitors in Phase 3
Pooled Phase 3 - PT Analysis Population

Drug	Rivaroxaban 10 mg qd (N=6093)
Any Pgp inhibitor	130
Cyclosporin	8
Erythromycin	8
Itraconazole	1
Ketoconazole	3
Quinidine	1
Verapamil	109

Phase 2 Simulations: Effect of Renal Impairment and Concomitant Use of CYP3A4 Inhibitors: Number of Subjects

Number of subjects	Normal Renal Function CLCR ≥80 mL/min	Mild Renal Impairment CLCR 50-79 mL/min	Moderate Renal Impairment CLCR 30-49 mL/min	All
5 mg dose group	62	48	13	123
10 mg dose group	76	58	6	140
20 mg dose group	66	52	13	131
All doses (5-10-20 mg)	204	158	32	394

Demographics Phase 2 comparable to Phase 3

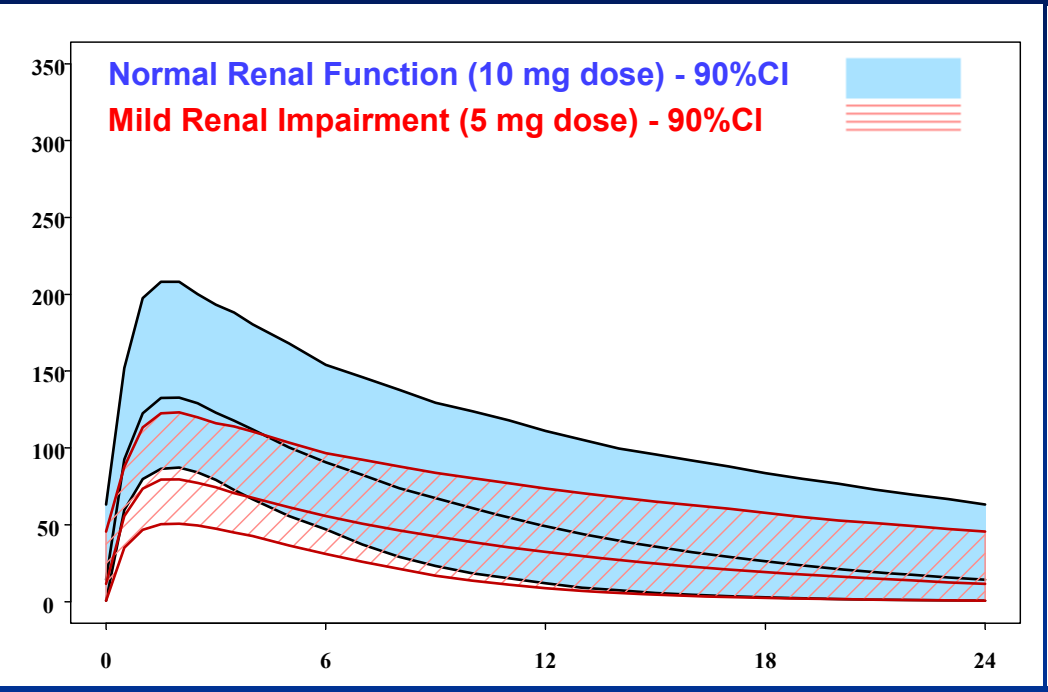
- mean age 64.0-65.0 years (for 5-10-20 mg dose groups) vs. 64.1 years (pooled RECORD 1-4)

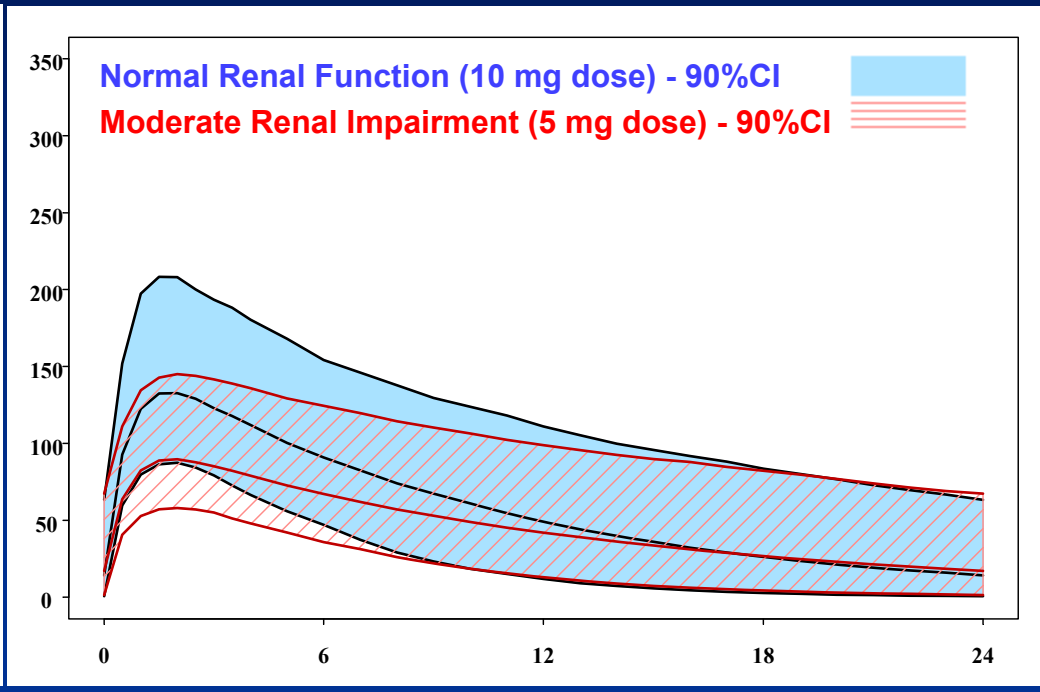
Phase 2 Simulations: Effect of Renal Impairment and Concomitant Use of CYP3A4 Inhibitors

- Patients from Phase 2 qd study (5-20 mg dose groups)
  - Categorized according to their CLCR values into: normal renal function (CLCR > 80 mL/min), mild (CLCR 50-79 mL/min) & moderate reduced renal function (CLCR 30-49 mL/min)
- Patient's total clearance derived from POP PK analysis
- Fraction CYP3A4 clearance vs. total clearance in patient population estimated based on ratio derived from renal impairment study
  - Assuming CYP 3A4 clearance = 23% of total clearance or 38% of hepatic clearance
    - fraction (11%) non-recovered & non-identified structures equally devided over CYP3A4 - CYP2J2 & non-CYP metabolism
- Simulations for different strengths of inihibition of CYP3A4
  - 30% - 50% en 86% (each with 20% variability)
- 1000 simulations for each of renal functions groups
  - re-sampling from 'real pool' of subjects

Predicted Steady State Plasma Concentration Window 5 mg qd in Phase 2 Target Population

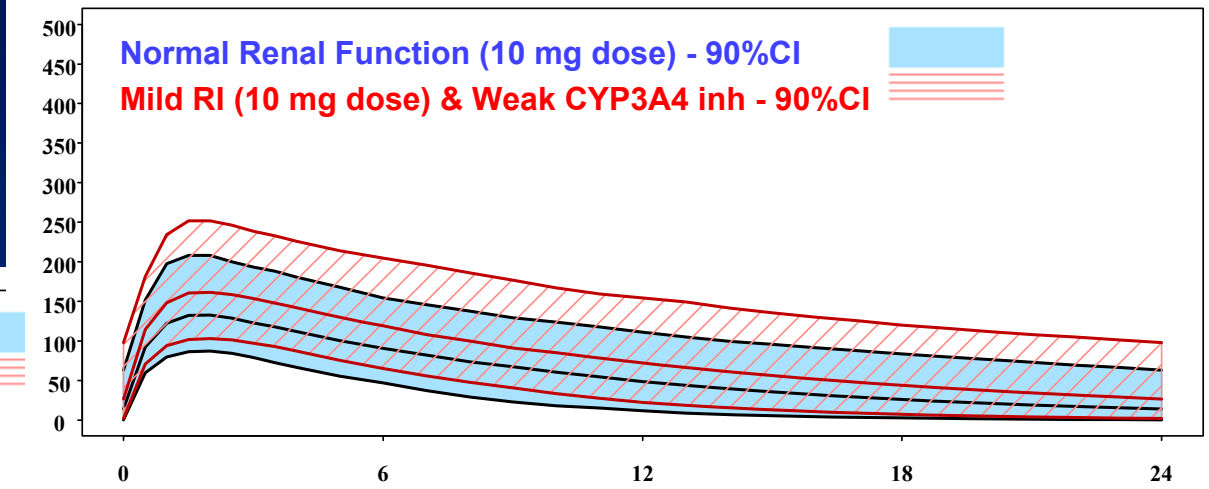
Normal Renal Function vs Mild and Moderate Renal Impairment

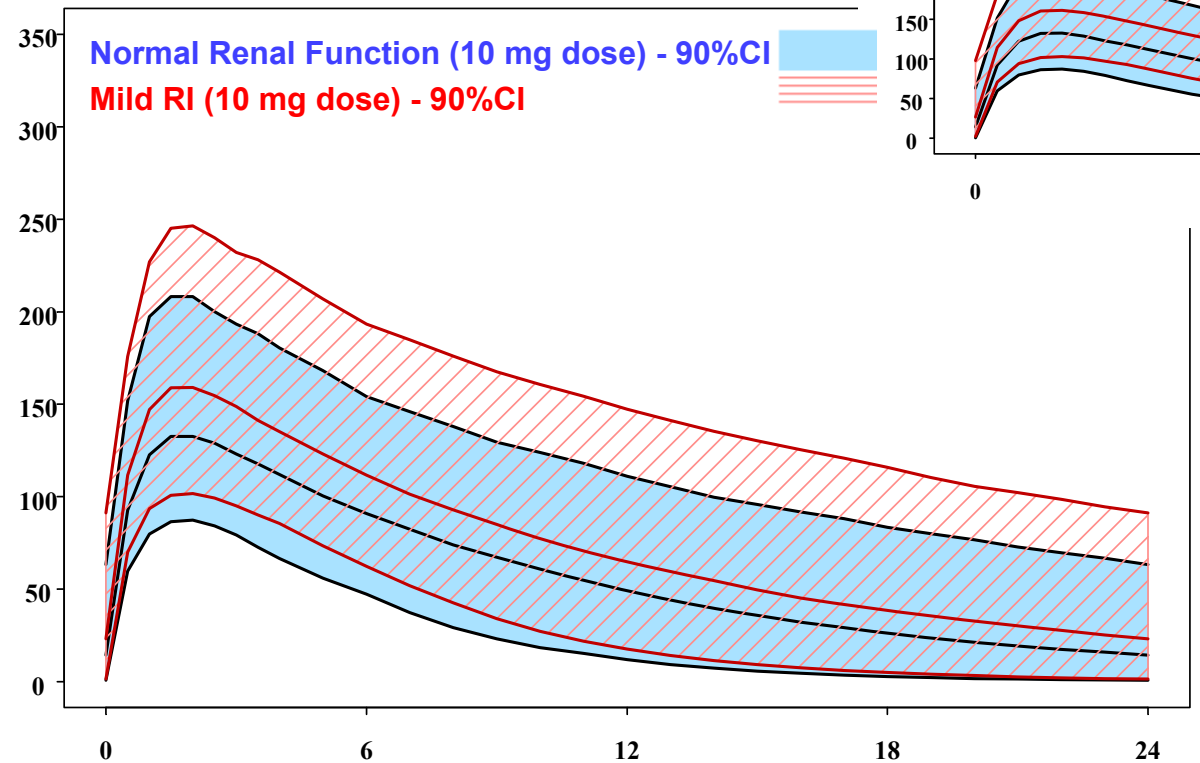




Predicted Steady State Plasma Concentration Window 10 mg qd in Phase 2 Target Population

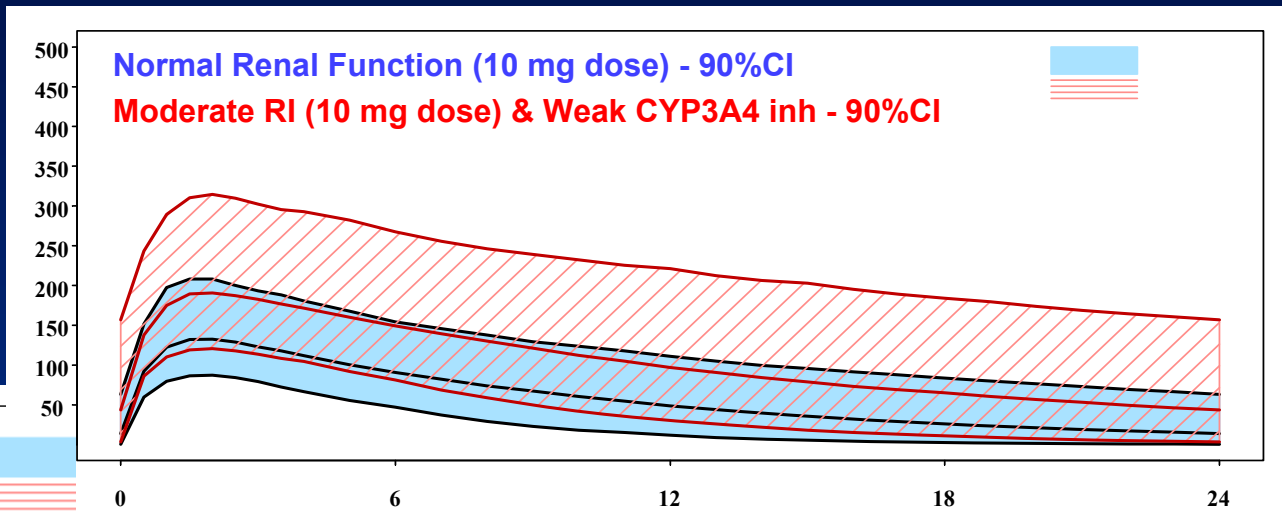
Mild Renal Impairment and Weak CYP 3A4 Inhibition

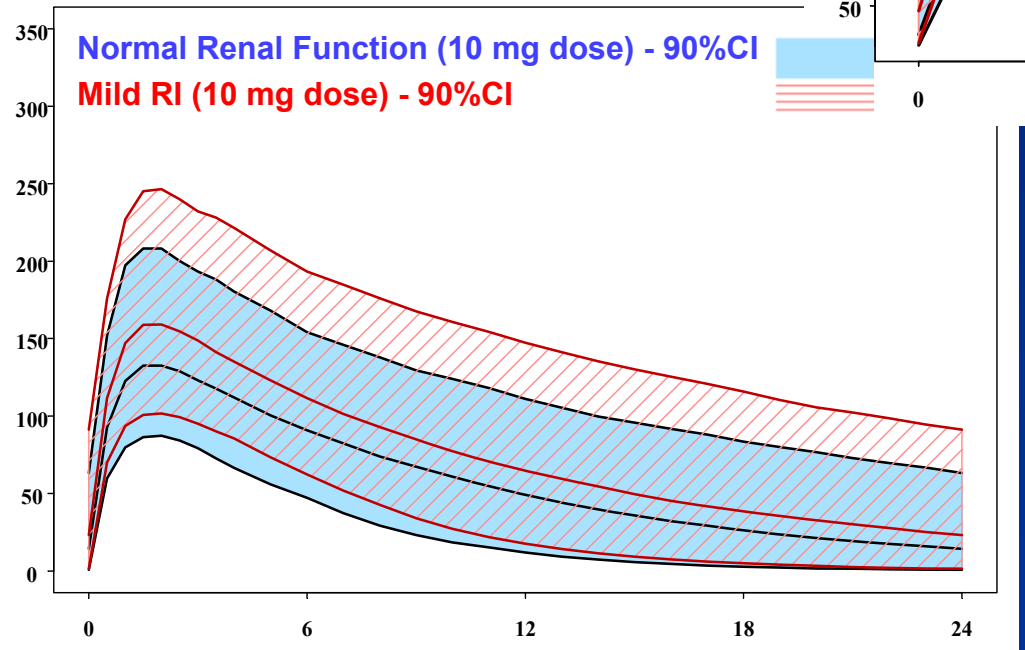




Predicted Steady State Plasma Concentration Window 10 mg qd in Phase 2 Target Population

Moderate Renal Impairment and Weak CYP 3A4 Inhibition





Phase 2 - Target Population -10 mg qd Simulations
Impact Renal Impairment and Concomitant CYP3A4 Inhibitor
x-fold Increase in AUC & C_{max}

	Normal Renal Function > 80 mL/min	Mild Renal Impairment 50-80 mL/min	Moderate Renal Impairment 30-50 mL/min
AUC			
No CYP3A4 inh	1.00	1.28	1.59
30% CYP3A4 inh	1.07	1.38	1.80
50% CYP3A4 inh	1.14	1.48	1.95
90% CYP3A4 inh	1.29	1.70	2.28
C_{max}			
No CYP3A4 inh	1.00	1.20	1.35
30% CYP3A4 inh	1.03	1.22	1.44
50% CYP3A4 inh	1.06	1.26	1.50
90% CYP3A4 inh	1.12	1.36	1.65

Phase 2 - Target Population
Impact Renal Impairment and Concomitant CYP3A4 Inhibitor x-fold Increase in AUC & C_{max}

5 mg rivaroxaban qd vs. 10 mg qd in subjects with normal renal function

	Normal Renal Function > 80 mL/min	Mild Renal Impairment 50-80 mL/min	Moderate Renal Impairment 30-50 mL/min
AUC			
No CYP3A4 inh	1.00	0.64	0.79
30% CYP3A4 inh	0.54	0.69	0.90
50% CYP3A4 inh	0.57	0.74	0.98
90% CYP3A4 inh	0.64	0.85	1.14
C_{max}			
No CYP3A4 inh	1.00	0.60	0.68
30% CYP3A4 inh	0.52	0.61	0.72
50% CYP3A4 inh	0.53	0.63	0.75
90% CYP3A4 inh	0.56	0.68	0.82

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/s/

Marcus Cato

4/27/2009 11:35:01 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Office of Surveillance and Epidemiology/through Janet Anderson	Marcus Cato, RPM, Division of Medical Imaging and Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
April 2, 2009		22-406	NDA	July 22, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xarelto (rivaroxaban) tablets	Rush	Anti-Xa	April 15, 2009

NAME OF FIRM: Johnson and Johnson Pharmaceutical Research & Development, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☒ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Please review the tradename Xarelto (rivaroxaban) tablets. Please find enclosed the proposed package insert and the proposed immediate container and carton labeling. (Note that the name was submitted to IND 64,892 on August 23, 2007 and to NDA 22-406 on August 26, 2008).

PDUFA DATE:
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA
HFD-160/Division File, HFD-160/RPM, HFD-160/Reviewers and Team Leaders

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Marcus Cato	☒ DFS ☒ EMAIL ☒ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

36 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Marcus Cato

4/2/2009 10:20:32 AM

Newman, Tyree

From: Greeley, George
Sent: Wednesday, March 25, 2009 3:39 PM
To: Cato, Marcus
Cc: Mathis, Lisa; Leaman, Diane V
Subject: NDA 22-406 Xarelto

Importance: High

Hi Marcus,

The Xarelto (rivaroxaban) full waiver was reviewed by the PeRC PREA Subcommittee on March 25, 2009. The Division recommended a full waiver because studies would be impossible or highly impracticable and because there are too few children with disease/condition to study. The PeRC agreed with the Division to grant a full waiver for this product.

It is also recommended that the Division request a consult with PMHS (Pediatrics and Maternal Health Staff) to determine if a Written Request for this product is feasible.

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

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/s/

TYREE L NEWMAN
07/01/2011

RECORD OF TELEPHONE CONVERSATION

NDA: 22-406/Rivaroxaban

Today's date: March 25, 2009

Speakers: Dwaine Rieves for FDA (prepped record)
Michael Kronig for J and J

Dr. Kronig had called and left a voice mail for me. I returned the telephone call and make the following notes:

-Dr. Kronig stated they looked forward to labeling discussions.

-I stated that reviews are on-going and I inquired about the status of the ATLAS 46 study report.

-Dr. Kronig stated they anticipated the Atlas study report "within a few weeks." Without questioning, Dr. Kronig stated that the company preferred lengthening the review cycle to receipt of a complete response letter. I stated that this aspect was a component of the review.

-Dr. Kronig stated that the sponsor would particularly like to discuss the clinical pharmacology and statistical aspects of the review with the review team. He noted that the sponsor preferred to have detailed discussions in which their statisticians talked with FDA statisticians. I stated we would look into the possibility but emphasized the challenges of schedules.

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/s/

Marcus Cato

3/30/2009 12:00:45 PM

CSO

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 16, 2009

TO: Marcus Cato, Regulatory Project Manager
Min Lu, Medical Officer
Division of Medical Imaging and Hematology Products

FROM: Susan D. Thompson, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Joseph Salewski
Deputy Division Director
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-406

APPLICANT: Johnson & Johnson

DRUG: Xarelto (rivaroxaban)

NME: Yes

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: 1. Prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery

CONSULTATION REQUEST DATE: April 28, 2009

DIVISION ACTION GOAL DATE: May 28, 2009

PDUFA DATE: May 28, 2009

I. BACKGROUND:

Rivaroxaban is a highly selective direct factor Xa (FXa) inhibitor for oral administration. Inhibition of FXa produces antithrombotic effects by decreasing the amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets,

without affecting existing thrombin levels. The sponsor states that the remaining thrombin should be sufficient to ensure primary hemostasis, resulting in a favorable efficacy to safety (bleeding) margin for rivaroxaban. The sponsor submits this NDA to support the use of rivaroxaban for the indication of prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery.
Patients undergoing major orthopedic surgery, including total hip replacement (THR) and total knee replacement (TKR) surgeries, are a group that is at a particularly high risk for venous thromboembolism (VTE), which includes DVT and PE. Without prophylaxis, the incidence of objectively confirmed total DVT based on older studies is approximately 40 to 60% following THR or TKR, with a 10-30% incidence of proximal DVT. The most appropriate strategy to reduce the incidence of VTE is prophylaxis for all patients undergoing THR or TKR. Current therapeutic agents available for anticoagulant prophylaxis include low molecular weight heparins (LMWHs), fondaparinux, and adjusted-dose vitamin K antagonists such as warfarin. The duration of therapy is at least 10 days for both THR and TKR; for patients undergoing THR, extended prophylaxis to up to 35 days after surgery is recommended. LMWHs and fondaparinux are administered subcutaneously, which may be associated with pain and bruising as well as poor compliance. Warfarin is the only available oral anticoagulant for VTE prophylaxis after major orthopedic surgery in the U.S. However, warfarin has a narrow therapeutic window, exhibits variable dose response, has many dietary and medicinal interactions, requires dose adjustment, and has a slow onset of action. Rivaroxaban offers an alternative oral prophylactic therapy for VTE.

IND 64,892 for rivaroxaban was submitted on May 29, 2002 for the treatment and secondary prophylaxis of VTE by Bayer. All of the clinical trials submitted with the current NDA were conducted by Bayer. Approximately one month prior to the submission of this NDA, Bayer sold the rights of reference for use of the investigations to Johnson and Johnson. Johnson and Johnson submitted NDA 22-406 as the applicant on July 28, 2008. Of note, both Bayer and Johnson and Johnson submitted letters to the review division that the IND is now transferred to Johnson and Johnson.

During the conduct of the clinical studies for this NDA, complaints were received regarding two investigators enrolling subjects, one in RECORD 2 and one in RECORD 4. A Warning Letter was issued to Dr. Arturo Corces on May 22, 2008 who enrolled subjects in RECORD 2 for failure to personally conduct or supervise the clinical investigations, failure to meet informed consent requirements, failure to ensure that studies were conducted according to the relevant current protocol, failure to maintain adequate and accurate case histories, and failure to maintain adequate drug disposition records. The Warning Letter to Dr. Corces from DSI recommended the data contributed to RECORD 2 by Dr. Corces by considered unreliable.
A NIDPOE is in progress for Dr. David Loucks, who enrolled subjects in RECORD 4. The Form FDA 483 describes failure to maintain accurate case histories including confirmed extensive falsification of the Principal Investigator's signature. Other violations noted were failure to report to the IRB all unanticipated problems involving risk to human subjects or others, the investigation was not conducted according to the investigational plan, and informed consent requirements were not met. On June 3, 2008, after discussion with the review division regarding the inspectional findings, Bayer notified the review division that due to falsification and systematic failures of the outpatient source data, that data from Dr. Loucks' site should be

excluded from the per protocol analysis. Bayer stated that since there was no evidence of data compromise during the inpatient phase of the study that this data from Dr. Loucks' site would be retained for the safety and MITT population; supplemental /sensitivity analyses were to be performed to explore the effect of removal of this site from these analyses. On the same date, Bayer notified the review division of a second RECORD 4 clinical investigator, Dr. Ricardo Esquivel in Naulcapan, Mexico, with issues impacting data integrity. These issues included inability to confirm from the source record that study medication was administered per protocol during the hospitalization periods, due to systematic discarding of medical records documenting study drug administration. The sponsor proposed to include data in the per protocol analysis for subjects who had electronic CRF entries verified from source data by the study monitor prior to destruction of source records.

Brief synopses of the protocols which the review division requested to be inspected are given below.

RECORD 1 Study: **Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE, controlled, double-blind, randomized study of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 1134)**

RECORD 1 was a randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national trial in patients undergoing elective THR conducted between February, 2006 and March, 2007. Subjects were enrolled at 218 centers in 27 countries. The objective of the study was to assess the safety and efficacy of rivaroxaban 10 my once daily compared with once daily subcutaneously administered enoxaparin 40 mg in extended prevention of VTE in men and women aged 18 years or above undergoing elective THA. Administration of BAY 59-7939 or placebo started on the day of surgery (Day 1) 6 to 8 hours after wound closure and thereafter once daily until Day 35 (the day before venography). Enoxaparin 40 mg was administered once daily as a subcutaneous injection starting the evening prior to surgery. Subsequently, enoxaparin or placebo was administered on the day of surgery 6 to 8 hours after wound closure and thereafter once daily until Day 35. Subjects were evaluated at Day 0, 1, 7 ($\pm$ 2 days), 13 ($\pm$ 2 days), and 36 ($\pm$ 4 days) with a follow-up visit at Day 65 ($\pm$ 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed, and a urine pregnancy test done for women of childbearing potential. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination was performed. On Day 7, physical examination and blood sampling for hematology and coagulation parameter were performed. On Day 13, physical examination and blood sampling for hematology and clinical chemistry were performed. On Day 36, blood samples for clinical chemistry, coagulation parameters, and hematology were taken, and bilateral venography was performed. Adverse events will be recorded at each visit. On Day 65, adverse events, signs and diagnosis of VTE, and cardiovascular and bleeding events during the 30 days after end of treatment will be recorded. Physical examinations were performed, and a blood sample for clinical chemistry was taken.
The primary efficacy endpoint was a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Venography and VTE Adjudication Committee. Secondary efficacy endpoints were major VTE, incidence of DVT, incidence of symptomatic VTE, incidence of symptomatic VTE during follow-up, "net clinical benefit", incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding occurring after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting more than 2 days after stop of treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, discontinuations due to adverse events, and laboratory parameters.

Brief Summary of Results

There were 4541 subjects randomized at 218 centers. Of these, 4433 subjects received study medication, and 3153 were valid for the modified intent to treat (MITT) analysis and 3029 were valid for the per-protocol (PP) analysis. In the PP analysis, 13/1537 (0.9%) subjects in the rivaroxaban arm met the primary efficacy endpoint and 50/1492 (3.4%) of subjects in the enoxaparin arm met the primary efficacy endpoint. These results demonstrated non-inferiority against enoxaparin using a non-inferiority margin of 3.5%. The results in the MITT population were similar, with the primary efficacy outcome reached by 18/1595 (1.1%) subjects in the rivaroxaban population and 58/1558 (3.7%) subjects in the enoxaparin population. This finding demonstrated statistical superiority (95% CI: -3.69%, -1.54%) of rivaroxaban over enoxaparin in preventing VTE. A total of 520 randomized subjects discontinued treatment prematurely (256 rivaroxaban subjects and 264 enoxaparin subjects). The most common reason for study withdrawal was withdrawal of consent: 121/ 2010 (5.3%) in the rivaroxaban arm and 115/2011 (5.1%) in the enoxaparin arm. The incidence of treatment-emergent major bleeding events was 0.3% in the rivaroxaban arm and <0.1% in the enoxaparin arm. There were no fatal bleeding events in either arm after start of study drug. There were 10 deaths in the study, 5 in each arm, and the incidence of treatment-emergent serious adverse events was similar between the 2 treatment groups (6.6% rivaroxaban, 8.1% enoxaparin).

RECORD 2 Study: **Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PPE controlled, double-blind, randomized study of BAY- 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement (Protocol 11357)**

RECORD 2 was a prospective, randomized, double-blind, double-dummy, active comparator controlled, multi-center and multi-national trial in patients undergoing elective THR conducted between February, 2006 and June, 2007. Subjects were enrolled at 123 active centers in 21 countries. The objective of the study was to compare the safety and efficacy of VTE prophylaxis with rivaroxaban 10 my once daily administered for 5 weeks to enoxaparin 40 mg

once daily administered for 10-14 days followed by placebo up to Day 35 in men and women aged 18 years or above undergoing elective THR. Administration of rivaroxaban or placebo started on the day of surgery (Day 1) at least 6 to 8 hours after wound closure and thereafter once daily every 24 ± 2 hours up to Day 35 ± 4 (the day before venography). All subjects in the rivaroxaban treatment group additionally received enoxaparin placebo subcutaneous injections once daily in the evening, starting on Day 0 and ending on Day 12 ± 2 (last dose). Enoxaparin 40 mg was administered once daily as a subcutaneous injection starting the evening prior to surgery (Day 0). Subsequently, enoxaparin or placebo was administered on the day of surgery 6 to 8 hours after wound closure and thereafter once daily until Day 12 ± 2. Additionally, all subjects in the enoxaparin group received rivaroxaban placebo tablets. The first rivaroxaban placebo tablet was taken on the day of surgery (Day 1), at least 6-8 hours after wound closure, and subsequently once daily every 24 ± 2 hours up to Day 35 ± 4. Subjects were evaluated at Day 0, 1, 7 (± 2 days), 13 (± 2 days), and 36 (± 4 days) with a follow-up visit at Day 65 (± 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed, and a urine pregnancy test done for women of childbearing potential. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination will be performed. On Day 7, physical examination and blood sampling for hematology and coagulation parameter were performed. On Day 13, physical examination and blood sampling for hematology and clinical chemistry were performed. On Day 36, blood samples for clinical chemistry, coagulation parameters, and hematology will be taken, and bilateral venography were performed. Adverse events will be recorded at each visit. On Day 65, adverse events, signs and diagnosis of VTE, and an assessment of cardiovascular and bleeding events during the 30 days after end of treatment were recorded. Physical examination will be performed, and a blood sample for clinical chemistry will be taken.
The primary efficacy endpoint was defined as a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Independent Central Adjudication Committee and VTE Adjudication Committees. The major secondary endpoint was the incidence of the composite endpoint comprising proximal DT, non-fatal PE, and VTE-related death. Additional secondary efficacy endpoints were incidence of symptomatic VTE, incidence of symptomatic DVT (total, proximal, distal), incidence of symptomatic VTE during follow-up, incidence of PE, incidence of death, “net clinical benefit”, incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding occurring after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting after treatment initiation up to 2 days after last study treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, discontinuations due to adverse events, and laboratory parameters.

Brief Summary of Results

There were 2509 subjects randomized at 123 centers. Of these, 2457 subjects received study medication, and 1733 were valid for the MITT analysis and 1615 were valid for the PP analysis. In the PP analysis, 11/812 (1.4%) subjects in the rivaroxaban arm and 66/803 (8.2%) of subjects in the enoxaparin arm met the primary efficacy endpoint. The results in the MITT population were similar, with the primary efficacy outcome reached by 17/864 (2.0%) subjects in the rivaroxaban population and 81/869 (9.3%) subjects in the enoxaparin population. This finding demonstrated statistical superiority (95% CI: -9.41%, -5.15%) of rivaroxaban over enoxaparin in preventing VTE. A total of 300 randomized subjects discontinued treatment prematurely (135 rivaroxaban subjects and 165 enoxaparin subjects). The most common reason for study withdrawal was withdrawal of consent in the rivaroxaban arm 51/1252 (4.1%) and adverse events in the enoxaparin arm 54/1257 (4.3%). The incidence of treatment-emergent major bleeding events was very low in both treatment groups (one subject each; <0.1%). There were no fatal bleeding events in either arm after start of study drug. There were 10 deaths in the study, 2 in the rivaroxaban arm and 8 in the enoxaparin arm, and the incidence of treatment-emergent serious adverse events was slightly higher in the enoxaparin group (10.7%) than in the rivaroxaban group (7.3%).

RECORD 3 Study: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 in the prevention of VTE in patients undergoing elective total knee replacement (Protocol 11356)

RECORD 3 was a prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multi-center and multi-national trial in patients undergoing elective TKR conducted between February, 2006 and January, 2007. Subjects were enrolled at 147 active centers in 19 countries. The objective of the study was to assess the safety and efficacy of rivaroxaban 10 mg once daily for the prevention of VTE in male and female subjects aged 18 years or above undergoing elective TKA. Administration of rivaroxaban or placebo started on the day of surgery (Day 1) 6 to 8 hours after wound closure, and continued once daily until Day 12 $\pm$ 2 (the day before venography). Enoxaparin 40 mg or matching placebo was administered once daily as a subcutaneous injection starting 12 hours prior to surgery (Day 0). Subsequently, enoxaparin or placebo was administered on the day of surgery at least 6 to 8 hours after wound closure and on subsequent evenings until the final evening dose administered on the evening of Day 12 $\pm$ 2. Subjects were evaluated at Day 0, 1, 7 ($\pm$ 2 days), and 13 ($\pm$ 2 days), with a follow-up visit at Day 42 ($\pm$ 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination was performed. On Day 7, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 13, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 42, adverse events, signs and diagnosis of DVT/PE were recorded. Physical examinations were performed, and a blood sample for clinical chemistry was taken. The primary efficacy endpoint was defined as a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Independent Central Adjudication Committee and VTE Adjudication Committees. The major secondary endpoint was the incidence of the composite endpoint comprising proximal DVT, non-fatal PE, and VTE-related death. Additional secondary efficacy endpoints were incidence of DVT (total, proximal, distal), incidence of symptomatic VTE (DVT, PE), incidence of symptomatic VTE during follow-up, "net clinical benefit" assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding, incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed no later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting after treatment initiation up to 2 days after last study treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, amount of intraoperative blood loss, postoperative volume of drainage, and laboratory parameters.

Brief Summary of Results

There were 2531 subjects randomized at 147 centers. Of these, 2459 subjects received study medication, and 1702 were valid for the MITT analysis and 1631 were valid for the PP analysis. In the PP analysis, 74/793 (9.3%) subjects in the rivaroxaban arm met the primary efficacy endpoint and 152/838 (18.1%) of subjects in the enoxaparin arm met the primary efficacy endpoint described by the sponsor as demonstrating noninferiority against enoxaparin, based on a noninferiority margin of 4%. The results in the MITT population were similar, with the primary efficacy outcome reached by 79/824 (9.6%) subjects in the rivaroxaban population and 166/878 (18.9 %) subjects in the enoxaparin population, described by the sponsor as demonstrating superiority of rivaroxaban over enoxaparin in preventing VTE (95% CI: -12.40%, -5.89%). A total of 282 randomized subjects discontinued treatment prematurely (127 rivaroxaban subjects and 155 enoxaparin subjects). The most common reason for study withdrawal was withdrawal of consent in both arms: 68/ 1254 (5.4%) in the rivaroxaban arm and 60/1277 (4.7%) in the enoxaparin arm. The incidence of treatment-emergent major bleeding events was low in both treatment groups (0.6% in the rivaroxaban arm versus 0.5% in the enoxaparin arm). There were no fatal bleeding events reported in either group. There were 6 deaths in the study, all in the enoxaparin arm. The incidence of treatment-emergent serious adverse events was slightly lower in the enoxaparin group (7.4%) than in the rivaroxaban group (8.9%).

RECORD 4 Study: **Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 (rivaroxaban) in the prevention of VTE in subjects undergoing elective total knee replacement (Protocol 11355)**

RECORD 4 was a prospective, randomized, double-blind, double-dummy, parallel-group, active comparator controlled, multi-center and multi-national trial in patients undergoing elective TKR conducted between June, 2006 and January, 2008. Subjects were enrolled at 131 active centers in 12 countries. The objective of the study was to assess the safety and efficacy of rivaroxaban 10 mg once daily for the prevention of VTE in male and female subjects aged 18 years or above undergoing elective TKA. Administration of rivaroxaban or placebo started on the day of surgery (Day 1) 6 to 8 hours after wound closure, and continued once daily until Day 12 $\pm$ 2 (the day before venography). Enoxaparin 30 mg bid or matching placebo was administered twice daily as a subcutaneous injection starting 12-24 hours after wound closure. Thereafter, enoxaparin active or placebo was administered subcutaneously twice daily, once in the morning and once in the evening (every 12 $\pm$ 2 hours), until the final evening dose administered on the evening of Day 12 $\pm$ 2 (the day prior to venography). Subjects were evaluated at Day 0, 1, 6 ($\pm$ 2 days), and 13 ($\pm$ 2 days), with a follow-up visit at Day 42 ($\pm$ 5 days). On Day 0 prior to surgery, a physical examination was performed, and medical history with demographics was recorded. Blood was sampled for clinical chemistry, hematology, and coagulation parameters. An ECG was performed. On Day 1, blood samples for hematology and clinical chemistry were taken after surgery but before study medication, and a physical examination was performed. On Day 6, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 13, physical examination and blood sampling for hematology, clinical chemistry, and coagulation parameters were performed. On Day 42, adverse events, signs and diagnosis of DVT/PE were recorded. Physical examinations were performed, and a blood sample for clinical chemistry was taken.

The primary efficacy endpoint was defined as a composite endpoint of:

- Any DVT (proximal and/or distal)
- Non-fatal PE
- Death from all causes

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Independent Central Adjudication Committee and VTE Adjudication Committees. The major secondary endpoint was the incidence of the composite endpoint comprising proximal DVT, non-fatal PE, and VTE-related death. Additional secondary efficacy endpoints were incidence of DVT (total, proximal, distal), incidence of symptomatic VTE (DVT, PE), incidence of symptomatic VTE during follow-up, "net clinical benefit" assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding, incidence of the composite endpoint that results from the primary endpoint by substituting VTE-related death for all death, and incidence of the composite endpoint that results from major VTE by substituting all-cause mortality for VTE-related death. The main safety endpoint was the incidence of treatment-emergent major bleeding observed no later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately. Also included as safety variables were treatment-emergent adverse events, serious adverse events, and deaths; adverse events starting after treatment initiation up to 2 days after last study treatment, adjudicated cardiovascular events, incidence of prolonged hospitalization, transfusion requirements, amount of intraoperative blood loss, postoperative volume of drainage, and laboratory parameters. Other safety variables included the incidence of any treatment-emergent bleeding observed no later than 2 days after last intake of study drug, the incidence of non-major

treatment–emergent bleeding observed no later than 2 days after last intake of study drug, incidence of postoperative bleeding, and incidence of surgical site bleeding associated with > 2 g/dL fall in hemoglobin or leading to infusion of > 2 units of whole blood or packed cells.

Brief Summary of Results

There were 3148 subjects randomized at 131 centers. Of these, 3034 subjects received study medication, and 1924 were valid for the MITT analysis and 1742 were valid for the PP analysis. In the PP analysis, 58/864 (6.7%) subjects in the rivaroxaban arm met the primary efficacy endpoint and 82/878 (9.3%) of subjects in the enoxaparin arm met the primary efficacy endpoint described by the sponsor as demonstrating noninferiority against enoxaparin, based on a noninferiority margin of 4%. The results in the MITT population were similar, with the primary efficacy outcome reached by 67/965 (6.9%) subjects in the rivaroxaban population and 97/959 (10.1%) subjects in the enoxaparin population, described by the sponsor as demonstrating superiority of rivaroxaban over enoxaparin in preventing VTE (95% CI: -5.67%, -0.71%). A total of 310 randomized subjects discontinued treatment prematurely (159 rivaroxaban subjects and 151 enoxaparin subjects). The most common reason for study withdrawal was adverse events in both arms: 62/ 1584 (3.9%) in the rivaroxaban arm and 56/1564 (3.6%) in the enoxaparin arm. The incidence of treatment-emergent major bleeding events was low in both treatment groups (0.7% in the rivaroxaban arm versus 0.3% in the enoxaparin arm). With regard to critical bleeding events, there was one retroperitoneal bleeding event (rivaroxaban), one intracranial bleed (enoxaparin), and one intraspinal/hemorrhagic puncture event (enoxaparin). There was one fatal bleeding event reported in the rivaroxaban treatment group. Twelve subjects died during the study, 6 in the rivaroxaban group and 6 in the enoxaparin group. The incidence of treatment-emergent serious adverse events was similar between the two groups: 5% in the rivaroxaban group and 7% in the enoxaparin group.

Rationale for Site Selection

Rivaroxaban is a new molecular entity which is an oral anticoagulant with the proposed indication of prophylaxis of VTE. The site selection is based on the review division's analysis of efficacy of rivaroxaban versus the comparator at individual sites. Sites which showed a greater efficacy of rivaroxaban in relation to comparator which had relatively high enrollment were chosen. Two sites for each of the pivotal studies were selected for inspection.

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol # and # of Subjects	Inspection Date	Interim Classification	Final Classification
Andrzej Gorecki Szpital Kliniczny Dzieciatka Jezus – Centrum Leczenia Obrazen Klinika Ortopedii i Traumatologii Narzadu Ruchu ul. Lindleya 4 02-005 Warszawa, POLAND	Protocol # 11354, RECORD 1 Site # Poland 18006 # of subjects (Total# 71): Xarelto: 36 Enoxaparin: 35	Pending	NAI	Pending
Tadeusz Gazdzik Slaska Akademia Medyczna Katedra I Oddzial Kliniczny Ortopedii Wojewodzki Szpital Specjalistyczny Nr 5 im. Sw. Barbaby Pl. Medykow 1 41-200 Sosnowiec, POLAND	Protocol # 11354, RECORD 1 Site # Poland 18012 # of subjects (Total#: 76): Xarelto: 38 Enoxaparin: 38	Pending	NAI	Pending
Qingming Yang Rui Jin Hospital, Shanghai Second Medical Univeristy Orthorpaedic Department Shanghai Ryuijin Hospital No. 197 Ruijin Second Road Shanghai, CHINA 200025	Protocol # 11357, RECORD 2 Site # China 54005 # of subjects (Total# 34): Xarelto: 17 Enoxaparin: 17	2/9-2/13/09	OAI	Pending
Cesar Diaz Valverde Hospital Edgardo Rebagliati Martins Av. Edgardo Rebagliati Martins S/N JESUS MARIALima Lima, 11 PERU	Protocol # 11357, RECORD 2 Site # Peru 64005 # of subjects (Total# 41): Xarelto: 20 Enoxaparin: 21	1/26-1/30/09	VAI	Pending
Bingfang Zeng Affiliated Sixth People's Hospital Orthorpaedic Department No. 600 Yishan Road, Xuhui District Shanghai, CHINA 200233	Protocol # 11356, RECORD 3 Site # China 54014 # of subjects (Total# 26): Xarelto: 13 Enoxaparin: 13	2/15-2/19/09	OAI	Pending
Jacek Kruczynski Szpital Uniwersytecki im. Antoniego Jurasze Klinika Ortopedii i Traumatologii Narzadu Ruchu ul. M. Sklodowskiej-Curie 9 85-094, Bydgoszcz POLAND	Protocol # 11356, RECORD 3 Site # Poland 18003 # of subjects (Total# 36): Xarelto: 18 Enoxaparin: 18	1/26-1/30/09	VAI	Pending

R. Michael Murray Capstone Clinical Research 2018 Brookwood Medical Center Suite 314 Birmingham, AL 35209	Protocol # 11355, RECORD 4 Site # 14005 # of subjects (Total # 152) Xarelto: 76 Enoxaprin: 76	2/17-2/26/09	Pending	Pending
David Fox Unlimited Research, LP 12709 Toepperwein Road Suite 101 San Antonio, TX 78233	Protocol #11355, Record 4 Site #14022 # of subjects (Total # 64) Xarelto: 32 Enoxaparin: 32	1/26-1/28/09, 2/2-2/6/09, 2/12-2/13/09	Pending	Pending
Bayer Pharmaceutical 340 Change Bridge Rd. Pine Brook, NJ 07058	Protocol # 11354, RECORD 1 Protocol # 11357, RECORD 2 Protocol # 11356, RECORD 3 Protocol #11355, Record 4	Pending	Pending	Pending
Johnson & Johnson 920 U.S. Highway 202 Raritan, NJ 08869-0602		Pending	Pending	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Andrzej Gorecki
Szpital Kliniczny Dzieciatka Jezus – Centrum Leczenia Obrazen
Klinika Ortopedii i Traumatologii
Narzadu Ruchu
ul. Lindleya 4
02-005 Warszawa, POLAND

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There was no screening log maintained at the site; all subjects listed in the Subject ID log were randomized. There were 71 subjects enrolled and 69 subjects completed the study; 1 subject discontinued due to withdrawal of consent and one subject discontinued due to a protocol violation (concomitant oral anticoagulant). The informed consent of all subjects were reviewed, and the medical file and venography films were verified for all subjects. The files of 20 subjects were reviewed/translated, with a review focus on adverse events. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no

limitations to the inspection.

b. **General observations/commentary**: No issues were noted with the Informed Consent Documents, record review, study drug accountability, or general conduct of the study. The primary efficacy endpoint was verifiable. No Form FDA 483 was issued to the investigator. The inspector notes that there was some underreporting of non-serious adverse events. The Sponsor was aware of this underreporting and allowed the investigator to report non-serious adverse events that were unexpected for the patient and/or atypical for the procedure. In addition, the dispensing log was completed in a retrospective manner; however, the actual administration log book was completed at administration.

c. **Assessment of data integrity**: The data from Dr. Gorecki's site appear acceptable for use in support of the NDA.

2. **Tadeusz Gazdzik**
Slaska Akademia Medyczna
Katedra I Oddzial
Kliniczny Ortopedii
Wojewodzki Szpital
Specjalistyczny Nr 5
im. Sw. Barbaby
Pl. Medykow 1
41-200 Sosnowiec, POLAND

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There was no screening log maintained at the site; all subjects listed in the Subject ID log were randomized. There were 76 subjects enrolled and 69 subjects completed the study; 4 subjects were discontinued due to withdrawal of consent, one subject was discontinued because surgery was not done, one subject discontinued due to a history of liver disease, and one discontinued due to a SAE (myocardial infarction). The informed consent documents of all subjects were reviewed, and the medical file and venography films were verified for all subjects. The files of 36 subjects were reviewed in part; 12 subject files had all progress notes translated, with a review focus on adverse events. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. **General observations/commentary**: No issues were noted with the Informed Consent Documents, record review, study drug accountability, adverse event reporting, or general conduct of the study. The primary efficacy endpoint was verifiable. No Form FDA 483 was issued to the investigator.

c. **Assessment of data integrity**: The data from Dr. Gazdzik's site appear acceptable for use in support of the NDA.

3. **Qingming Yang**
Rui Jin Hospital, Shanghai Second Medical University
Orthorpaedic Department
Shanghai Ryuijin Hospital
No. 197 Ruijin Second Road
Shanghai, CHINA 200025

a. **What was inspected**: The inspection was conducted in accordance with Compliance Program 7348.811. There were 34 subjects screened at the site, and all 34 were enrolled. There were 23 subjects who completed the study. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. In addition, a letter responding to the Form FDA 483 dated March 3, 2009 from Dr. Yang was reviewed as well as an affidavit generated during the inspection by a subinvestigator, (b) (6) . An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. **General observations/commentary**: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60, failed to report to the sponsor adverse events, in violation of 21 CFR 312.64, did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b), failed to include contact information for subject questions in the Informed Consent Document (ICD), in violation of 21 CFR 50, and failed to include in the ICD the possibility that the FDA may inspect the study records.

<u>Protocol Violations [21 CFR 312.60]</u>

1. The Principal Investigator (PI) did not ensure that all associates and colleagues assisting in the investigation were meeting the commitments of the study protocol and regulations. Sub-Investigator (b) (6) was discovered to have recorded a Visit on Day 65 for Subject 54005-7005 (b) (6) However, Sub-Investigator (b) (6) contacted the subject and confirmed that the patient visit never took place; according to the inspector, the visit was struck out in the record. However, there was no further investigation into this incident, nor into whether the same issue may emerge in other subject records. An affidavit was taken from the Sub-Investigator regarding this incident; the PI also addressed this incident in a letter responding to all the findings listed in the Form FDA

483. However, the versions of this incident in the affidavit and the letter are not the same.

Adverse Event Reporting [21 CFR 312.64]

1. There were two subjects (54005-7021 (b) (6) and 54005-7006 (b) (6)) who experienced a ≥ 2 g/dL drop in hemoglobin requiring transfusion of 400 mL of Red Blood Cells (RBCs) and 200 mL of Fresh Frozen Plasma (FFP). Two additional subjects (54005-7005 (b) (6) and 54005-7017 (b) (6)) had a ≥ 2 g/dL drop in hemoglobin and received transfusion of RBCs and FFPs. None of these were reported as adverse events. In his response letter the PI states that blood loss and transfusion is normal for a subject post orthopedic surgery and therefore was not considered an adverse event. However, the definition of adverse events contained in the protocol does not exclude such conditions.

   Medical Officer Comment: It is possible that these adverse events were reported as "Bleeding Events", a safety variable in this study. However, such reporting does not obviate the requirement to report them as adverse events, as the protocol does not exclude postoperative conditions.
2. There were two subjects (54005-7020 (b) (6) and 54005-7012 (b) (6)) with elevations of AST and/or ALT of 1.5 to > 3 times the upper limit of normal on several occasions which were not reported as Adverse Events.
3. Subject 54005-7021 experienced nausea which was not reported as an adverse event.
4. Subject 54005-7006 experienced constipation for 3 days which was not reported as an adverse event.
5. Subject 54005-7005 had a decreased albumin on two occasions (Day 3 and Day 7) for which albumin infusions on Day 5 and Day 6 were administered.

Recordkeeping Violations [21 CFR 312.62(b)]

1. There is no source data maintained by the Clinical Investigator (CI) of the actual investigational drug administration times for all subjects. The CI assumes that the study nurse administers IV and oral doses according to the Long-Term orders in the medical records. The PI's response indicates that this procedure is standard Chinese medical practice, and that nurses maintain their own temporary notes regarding drug administration which are later discarded.
2. The CI did not maintain a complete copy of the informed consent forms for all subjects; only the last two pages were retained in the subject record for Subjects 54005-7021 (b) (6), 54005-7029 (b) (6) 54005-7030 (b) (6) 54005-7032 (b) (6), 54005-7033- (b) (6), and 54005-7034 (b) (6).
3. Source documents for Day 36 and 65 were not always completed and signed by the Sub-investigator completing the forms, and they were not reviewed by the PI. These source documents included In-Patient Study

Drug Administration, Adverse Event Reports, Blood Transfusion, Drug Administration After-Discharge, and end of treatment records for Subjects 54005-7004 (b) (6) 54005-7005 (b) (6), 54005-7012 (b) (6) 54005-7020 (b) (6), and 54005-7021 (b) (6).

Informed Consent Violations [21 CFR 50]

1. The version of the ICD signed by all 33 subjects lacked the contact information of the CI and the IRB/EC. This version of the IC was approved by the IRB/Ethics Committee.
2. The ICD signed by all 33 subjects enrolled in the clinical trial did not include the statement that the U.S. FDA may inspect the study records.

c. **Assessment of data integrity**: There were protocol, adverse event reporting, recordkeeping, and informed consent violations reported from this site. Of most concern is the apparent falsification of data by a subinvestigator for a patient visit. However, of even more significance is that there was no investigation into this incident by the PI or his representative, and the Sub-investigator who entered the erroneous data continued to perform study-related procedures. Lastly, the lack of consistency between the Sub-Investigator's affidavit and the PI's letter raises concern regarding the veracity of the information provided. In addition, there appears to be significant underreporting of adverse events from this site, including anemia/bleeding requiring transfusion and liver function abnormalities. DSI recommends that the data from subjects enrolled in RECORD 2 at Dr. Yang's site not be considered acceptable for use in support of the NDA. In addition, any data obtained from subjects enrolled in RECORD 3 at this site should also be regarded as unreliable. Although data from RECORD 3 at Dr. Yang's site was not audited, the Sub-investigator in question may have participated in study activities, and the lack of oversight appears to be significant at this clinical trial site.

4. **Cesar Diaz Valverde**
Hospital Edgardo Rebagliati Martins
Av. Edgardo
Rebagliati Martins S/N
JESUS MARIALima
Lima, 11 PERU

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 41 subjects enrolled at the site; a screening log was not maintained. There were 39 subjects who completed the study; 1 subject withdrew due to a SAE and 1 subject withdrew consent. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60 and did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b).

Protocol Violations [21 CFR 312.60]

1. The following adverse events were not reported as required by the protocol: Subject 7001 – abdominal distention, nausea, and vomiting; Subject 7002 – constipation and nausea; Subject 7004 – sore throat; Subject 2006 – short of breath; Subject 7012 – headache and gastric discomfort; Subject 7026 – headache; blurred vision, vertigo, and vomiting; Subject 7036 – gluteal dermatitis and cough; Subject 7038 – liquid stools; rash and itching; headaches on 3 occasions; Subject 7039 – nausea and 2 episodes of chest pain; and Subject 7041 - gastric discomfort.
2. The following concomitant medications were not documented: Subject 7001 – Glycerin suppository; Subject 7002 – Glycerin suppository; and Subject 7008 – Timolol eye drops.
3. Subject 7009 did not have a 12 lead ECG printout in the medical or source records, although the CRF indicates that one was done.
4. The protocol requires that venography studies (performed for DVT diagnosis) be done in the respective hospital radiology unit. The subjects at this site did not have the bilateral venography performed at the respective hospital radiology unit, and there is no documentation for the CI fully explaining this deviation.
5. There was no source documentation for the receipt of the Coagulation blood samples by the (b) (4) for Subject 7024 on Day 0.
6. The source hospital medical record for Subject 7013 was not available for the inspector's review and was reported to be lost from the central archive.

Recordkeeping Violations [21 CFR 312.62(b)]

1. The source hospital medical record for Subject 7013 was not available for the inspector's review and was reported to be lost from the central archive.
2. Subject 7009 did not have a 12 lead ECG printout in the medical or source records, although the CRF indicates that one was done.
3. There was no source documentation for the receipt of the Coagulation blood samples by the (b) (4) for Subject 7024 on Day 0.

c. **Assessment of data integrity**: Although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. However, significant underreporting of adverse events at this site raises the question of whether the rights, safety, and welfare of any of the randomized subjects

was compromised due to these inaccuracies. The data appear acceptable for use in support of the NDA.

5. **Bingfang Zeng**
Affiliated Sixth People's Hospital
Orthorpaedic Department
No. 600 Yishan Road,
Xuhui District
Shanghai, CHINA 200233

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 26 subjects enrolled at the site. There were 23 subjects who completed the study. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60 and did not promptly report to the sponsor adverse effects that may reasonably be regarded as caused by or probably caused by, a investigational drug, in violation of 21 CFR 312.64.

Protocol Violations [21 CFR 312.60]

1. Two subjects were administered prohibited concomitant medications while enrolled in the clinical trial. Subjects 54014-6001 (b) (6) and 54014-6014 (b) (6) were treated with Salvia Miltiorrhiza (a platelet inhibitor) from Day 7 to Day 13 and on Day 2, respectively.
2. Subject 54014-6001 was treated with Aescuven Forte which was not listed on the concomitant drug list (eCRF) .

Adverse Event Reporting [21 CFR 312.64]

1. Two subjects did not have SAEs reported within 24 hours of the investigator's awareness of the event.
    i. Subject 54014-6007 was diagnosed with a DVT in the right leg on June 27, 2006. This SAE was not reported to the Sponsor until March 2, 2007 and the IRB/EC until March 19, 2007.
    ii. Subject 54014-6014 (b) (6) was diagnosed with a DVT in the right calf on October 6, 2006. The SAE was not reported to the Sponsor and the IRB/EC until October 11, 2006.
2. Multiple subjects did not have adverse events reported to the sponsor, although the concomitant medications they received for these conditions were recorded. These include Subject 54014- 6001 (b) (6) – swelling and

decreased albumin levels; Subject 54014-6006 (b) (6) – swelling at the incision site; Subject 54014-6009 (b) (6) – phlegm/sputum production; Subject 54014-6012 (b) (6) – insomnia; Subject 54014-6013 (b) (6) – constipation and phlegm; Subject 54014-6014 (b) (6) – trophic nerve on two occasions and blood vessel constriction; Subject 54014-6015 (b) (6) chest stress and phlegm; Subject 54014-6018 – fever and decrease in hemoglobin; Subject 54014-6020 (b) (6) – "dephlogisticate", fever, and wound swelling; Subject 54014-6023 (b) (6) – stomach pain.

c. Assessment of data integrity: Although protocol and adverse event reporting violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. However, significant underreporting of adverse events at this site raises the question of whether the rights, safety, and welfare of any of the randomized subjects was compromised due to these inaccuracies. The data appear acceptable for use in support of the NDA.

6. **Jacek Kruczynski**
Szpital Uniwersytecki im.
Antoniego
Jurasze
Klinika Ortopedii i Traumatologii
Narzadu Ruchu
ul. M. Sklodowskiej-Curie 9
85-094, Bydgoszcz
POLAND

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 36 subjects enrolled at the site; there was no screening log at the site. There were 34 subjects who completed the study; 2 subjects did not have surgery. The informed consent documents of all subjects were reviewed, and the medical file and venography films were verified for all subjects. The progress notes in the files of 13 subjects were translated and reviewed. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: Several deviations from FDA regulations were noted, and a Form FDA 483 was issued for these violations. The inspection documented that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60.

Protocol Violations [21 CFR 312.60]

1. Subjects were randomized prior to required screening activities. Subjects 6006, 6010, 6011, 6012, 6014, 6019, 6020, and 6025 were randomized prior to obtaining subjects' ECG's and/or blood sampling for hematology, clinical chemistry, coagulation parameters, and serology retention sample.
2. ECG interpretation by Internal Medicine/Cardiology was not implemented/recorded in source documentation until approximately June, 2006. ECGs performed prior to this time were retrospectively reviewed and documented for source/CRF entry.
3. Investigational drug disposition records were not adequate with respect to dates, quantity and use by subjects in source subject drug administration records (temperature charts) were completed by subinvestigators not administering or witnessing the administration of the study drugs. The records do not document the identity and signature of administering/dispensing person.

   Medical Officer's Comment: The inspector notes in an accompanying email that the actual administration log book at the site was completed at administration. Therefore, although this citation represents a protocol violation, it does not affect data integrity.

c. Assessment of data integrity: Although protocol violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

7. R. Michael Murray
Capstone Clinical Research
2018 Brookwood Medical Center
Suite 314
Birmingham, AL 35209

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 178 subjects who signed informed consent at the site, and 153 were randomized. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: The inspection documented that the investigator did not prepare and maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation, in violation of 21 CFR 312.62(b), and did not adhere to the investigational plan, in violation of 21 CFR 312.60.

Recordkeeping Violations [21 CFR 312.62(b)]

1. Subject 5117 experienced an elevated lipase. Site email dated 7/2/07 from Capstone Clinical Trials, Inc. President/CEO to the monitor reported that the subject "was receiving rivaroxaban in the Bayer 11355 trial". The inspector's review of the study records failed to reveal how the site became awar of the Subject's blinded treatment assignment. No documentation was observed of sponsor or site emergency unblinding of this subject.
2. The site lacked documentation of IRB approval of the following:
    i. The performance of study screen visits at locations outside of routine clinical settings and not listed on the Form FDA 1572. For example screening visits including physical exams, ECGs, blood draws, etc. were conducted in subjects' homes and hotel rooms.
    ii. The performance of post-enrollment study visits that included physical exams and administration of the test article at sites not listed on the Form FDA 1572 not under the PI's supervision. Subjects were sometimes moved to an inpatient rehabilitation facility together with the test article where it was dispensed and administered by the rehab center staff who had not received training on the protocol or GCP. Study visits were also conducted at subject's homes after the subjects had been discharged from the hospital, including the article administration, physical exams, and blood draws. These alternate sites included the site's sister company, [redacted] (b) (4), the subject's place of employment, and an outpatient physical therapy center.
    iii. Payment/reimbursement of subjects' hotel stays, mileage, and transportation costs like cab fares, despite the IRB-approved informed consent which states "the maximum total possible payment is $250.00". The consent document does not mention additional services/reimbursement.
3. The site lacked documentation that the Final Report/notice of study closure was submitted to the IRB (or that the Board acknowledged receipt of the final report/study closure). A copy of the site's computer version of the Final Report dated 4/24/08 that is unsigned/unofficial was provided during the inspection; however, there is no documentation that this report was submitted to the board.
4. The most recent status report submitted to the IRB was the Annual Review Report dated 6/26/07 and signed by the PI states in Item #8 that the site is currently enrolling patients in this study. In Item #9 it states that "this study is closed to further enrollment". In addition, the following statement was included: ". . . as this study is no longer open to enrollment. No further subjects will be consented.". According to the site enrollment logs, subjects were enrolled/randomized through 10/9/07.
5. The site Signature Sheet and Delegation of Duties Log is inaccurate in that the Log does not reflect the performance of physical exams by the Physician Assistants (who routinely conducted physical exams throughout the study). At least one physical exam was performed by an RN/study coordinator per

source records. RNs are not licensed to conduct physical exams in the state of Alabama.

Protocol Violations [21 CFR 312.60]

1. Subjects were randomized post-surgery rather than prior to surgery. According to the protocol, randomization was to take place following screening on Day 0 or prior to surgery on Day 1.

c. Assessment of data integrity: Although protocol and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

8. David Fox
Unlimited Research, LP
12709 Toepperwein Road
Suite 101
San Antonio, TX 78233

a. What was inspected: The inspection was conducted in accordance with Compliance Program 7348.811. There were 72 subjects screened at the site, and 64 were enrolled. There were 60 patients who completed the study. During the inspection, 23 subject records were reviewed, and all 72 informed consent documents were reviewed. The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. There were no limitations to the inspection.

b. General observations/commentary: The inspection documented that the investigator did not obtain informed consent in accordance with 21 CFR 50 from each human subject prior to drug administration and that the investigator did not adhere to the investigational plan, in violation of 21 CFR 312.60.

Informed Consent Violations [21 CFR 50]

1. The CI failed to obtain informed consent from each human subject prior to drug administration and conducting study related tests.
    i. Subjects 5070 signed an informed consent document on September 13, 2007 that had expired on September 12, 2007, and did not sign the next approved version.
    ii. Subject 5071 signed an informed consent document on September 19, 2007 that had expired on September 12, 2007. This subject then signed the next approved version of the consent form on September 25, 2007.
2. The CI failed to have Subjects 5046, 5047, 5049, 5066, and 5068 sign a new version of the informed consent document after the original signed informed consent document is superceded.

Protocol Violations [21 CFR 312.62(b)]

1. According to the protocol, on Day 0 (the day prior to surgery), the subject will be randomized if eligible for the study. All 23 subjects reviewed were randomized on Day 1 instead of Day 0.
2. According to the protocol, on Day 6 ± 2, blood sampling for hematology, clinical chemistry, and coagulation parameters was to be done for all subjects. Subject 5003 and 5010 did not have their coagulation parameters drawn in the correct timeframe.
3. The visit for Study Day 42 was conducted out of the visit window (Day 42 ± 5) for the following subjects: Subject 5003 – 3 days out of window; Subject 5010 – 2 days out of window; Subject 5011 - 2 days out of window; Subject 5018 – 2 days out of window; Subject 5024 – 3 days out of window; Subject 5025 – 2 days out of window; Subject 5041 – 2 days out of window; and Subject 5060 – 4 days out of window.
4. There were no Protocol Deviation Reports submitted to the IRB for any of the violations described in Parts 1-3 above.

c. Assessment of data integrity: Although informed consent and recordkeeping violations occurred at this site, it is unlikely that these errors will impact the final outcome of the study. The data appear acceptable for use in support of the NDA.

9. **Sponsor/Monitor/CRO**
   Bayer Pharmaceutical
   340 Change Bridge Rd.
   Pine Brook, NJ 07058

   a. **What was inspected**: This inspection is ongoing; no information regarding the results of the inspection has been received.

9. **Applicant**
   Johnson & Johnson
   920 U.S. Highway 202
   Raritan, NJ 08869-0602

   a. **What was inspected**: This inspection has not yet been conducted.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, inspection of the Drs. Gorecki, Gazdzik, Kracznski, Murray, and Fox sites revealed that they adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations. The inspection of documents supports that audited subjects exist, met eligibility criteria, received assigned study medication, adhered to protocol, and signed informed consent documents. The inspections documented minor regulatory violations at the sites of Drs. Gorecki, Gazkzik, Kracznski, Murray, and Fox regarding protocol, recordkeeping, and informed consent violations. In general, the studies at these sites appear to have been conducted adequately, and the data generated by these sites may be used in support

of the indication. The results of the inspection of the sponsor Bayer Pharmaceuticals are not yet available, and the inspection of the applicant Johnson & Johnson has not yet taken place.

The inspection of Dr. Valverde's and Dr. Zeng's site raise concern regarding underreporting of adverse events. Although neither site appears to have failed to report serious adverse events, the number of unreported adverse events is significant. The data from these sites appear acceptable for use in the NDA.

Of greatest concern are the findings of the inspection of Dr. Yang's site. The inspector describes an instance of apparent falsification of a subject visit by a sub-investigator, which was reportedly detected later by a second investigator. However, there was no investigation into the circumstances of the falsification incident, and the Sub-Investigator was allowed to continue to administer the study. In addition, the affidavit provided by the second subinvestigator at the time of the inspection and the response letter from the PI give two different versions of this event. Lastly, there is no evidence that this discrepancy was detected by the study monitor. There were four instances of unreported anemia requiring transfusion and two unreported instances of elevated liver function tests from this site. It is possible that the anemia requiring transfusions was reported as the safety variable "Bleeding event"; however, these should also have been recorded as adverse events. DSI recommends that data from this site be regarded as unreliable.

At the present time, we cannot comment on the adequacy of clinical trial monitoring by the sponsor and the CRO (b) (4) When the sponsor inspection is completed and the results transmitted to DSI, we will generate an inspection summary addendum.

Follow-Up Actions: All observations above are based on preliminary communications with the FDA Field investigators and the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR. For the ongoing and pending inspections, an inspection summary addendum will be generated after the inspections have been completed and the results have been evaluated by DSI.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Joseph Salewski
Deputy Division Director
Division of Scientific Investigations

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Susan Thompson
3/16/2009 03:11:52 PM
MEDICAL OFFICER

Joseph Salewski
3/17/2009 01:37:09 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on March 13, 2009. The purpose of the meeting was to discuss the upcoming advisory committee (AC) meeting.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: March 13, 2009
TIME: 3:00 PM - 4:00 PM EST
LOCATION: CDER WO 2376 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., Clinical Reviewer
Diane Leaman, Safety Project Manager

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS VII

Chava Zibman, Ph.D., Statistical Reviewer

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/
PHARMACOMETRICS DIVISION

Christoffer Tornoe, Ph.D., Clinical Pharmacology Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader

EXTERNAL ATTENDEES:

JOHNSON & JOHNSON

Peter DiBattiste	M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters	M.D. Franchise Medical Leader
Lloyd Haskell	M.D. VP, CDTL
Leonard Oppenheimer	Ph.D. Statistical Sciences
Mehul Desai	M.D. Clinical
Jesse A. Berlin	ScD, VP, Epidemiology
G.K. (Dina) Anand	M.D., Post-Marketing Safety Franchise Leader
Michael Kronig	M.D. , VP Cardiovascular Regulatory Affairs
Sanjay Jalota	MRPharmS, Regulatory Global Regulatory Lead
Donald L. Heald	Ph.D. VP and Global Head of Clinical PK
Achiel Van Peer	Ph.D. Global Sr. Scientific Leader Clinical Pharmacology
An Thyssen	Ph.D. Clinpharm Leader Rivaroxaban
Harry Flanagan	DO, Post-Marketing Safety Expert, Benefit Risk Management
Sigmond Johnson	MS, MBA Program Coordinator
John Zhang	Ph.D. Statistical Sciences

BAYER

Frank Misselwitz	M.D. , Ph.d., VP Head Therapeutic Area CV & Coagulation
Scott D. Berkowitz	M.D. FACP, FACC, VP, Head, Thrombosis & Hemostasis CV and Coagulation
Gerhard Schlueter	Regulatory Head of General Medicine/Cardiology
Alice Benson	Principal Statistician, Global Clinical Statistics
Patricia Hagerty	Statistical Analyst –Global Statistical Programming
Larry Winick	MA Global Regulatory Strategist; Hematology/Cardiology
Dagmar Kubitza	Ph.D. Global Clinical Pharmacology Project Leader
Torsten Westermeier	Ph.D. Therapeutic Area Expert Statistician CC
Aasia Bhatti	M.D. Deputy Director for Int'l Drug Safety Division
Bernard Glombitza	M.D. Global Project Leader Wuppertal, Germany
Harald Kallabis	
Wolfgang Muerk	

BACKGROUND:

N/A

MEETING OBJECTIVES:

To provide clarifications regarding FDA presentations and discuss expectations for the March 19, 2009, advisory committee meeting (AC).

DISCUSSION POINTS:

FDA provided an overview of their expectations for the AC. FDA emphasized that all its comments are subject to change. In general FDA expects:

- Introductory Comments- Dr. Rieves (5 minutes)
- Sponsor Speakers (1.5 hours)
- Questions to Sponsor
- Break
- FDA Presentations
    - Overview of Prophylaxis of Deep Vein Thrombosis and Pulmonary Embolism Treatment in Patients Undergoing Hip or Knee Replacement Therapy (10 min).
    - Safety and Efficacy of Xarelto for prophylaxis in patients undergoing hip or knee replacement surgery— (30 minutes)
    - Statistical Analysis Considerations (10 min)
    - Hepatotoxicity Concerns (15 min)
    - Dose Adjustment Considerations (10 min)

FDA does not anticipate an emphasis upon efficacy in the FDA presentation. The main FDA presentation will predominantly relate to safety. FDA questions to the AC will likely be about the utility of a lower dose for special populations, if the data identify a risk for liver toxicity, the importance of ongoing data in the characterization of safety and the overall risk/benefit assessment.

J&J discussed its plans and mentioned their comments are subject to change as their process is fluid also. At the moment J&J plans to present:

- The current state of prophylaxis of DVT in orthopedic surgery in the context of the US and the rest of the world,
- The trail data with emphasis on efficacy, and safety
- A substantial liver presentation
- The overall risk/benefit assessment.

DECISIONS (AGREEMENTS) REACHED:

- N/A

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- N/A

ACTION ITEMS:

- N/A

ATTACHMENTS/HANDOUTS:

- N/A

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marcus Cato

3/18/2009 12:16:02 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: PEDIATRIC AND MATERNAL HEALTH STAFF (CDER/OND/PMHS)/ through George Greeley	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Marcus Cato, RPM, Division of Medical Imaging and Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 13, 2009	N/A	22-406	background info for the PeRC meeting	N/A

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xarelto™ (Rivaroxaban) Tablets	Rush	Factor Xa inhibitor	March 25, 2009

NAME OF FIRM: Johnson and Johnson (J&J)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: background info for the PeRC meeting

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

DMIHP requests PMHS to review the background materials and attend the PeRC meeting for Xarelto NDA 22-406 scheduled 3/25/09.

SIGNATURE OF REQUESTOR Marcus Cato, RPM, Division of Medical Imaging and Hematology Products	METHOD OF DELIVERY (Check one) ☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-406 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name:DMIHP PDUFA Goal Date: 5/28/09 Stamp Date: 7/28/2008

Proprietary Name: Xarelto

Established/Generic Name: rivaroxaban

Dosage Form: tablets

Applicant/Sponsor: Johnson and Johnson Pharmaceutical Research & Development, LLC

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) _____
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):2
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing hip replacement surgery

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☒ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☒ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4)

additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing knee replacement surgery

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☒ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☒ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☒ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☒ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☒ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the

drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:			
Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

Pediatric Research and Equity Act Waivers

NDA #:22-406 Supplement Type: N/A Supplement Number: N/A

Product name and active ingredient/dosage form: Xarelto (Rivaroxaban) Tablets

Sponsor: Johnson & Johnson

Indications(s): Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing hip replacement surgery
(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

1. Pediatric age group(s) to be waived. Birth to age 16 years.

2. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

    a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

Indications(s): Prophylaxis of deep vein thrombosis and Pulmonary embolism in patients undergoing knee replacement surgery
(NOTE: If the drug is approved for or Sponsor is seeking approval for more than one indication, address the following for each indication.)

3. Pediatric age group(s) to be waived. Birth to age 16 years.

4. Reason(s) for waiving pediatric assessment requirements (choose all that apply **and provide justification**):

    a. Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). If applicable, chose from adult-related conditions in Attachment I

Attachment I

<u>Adult-Related Conditions that do not occur in pediatrics and qualify for a waiver</u>
These conditions qualify for waiver because studies would be impossible or highly impractical

Age-related macular degeneration
Alzheimer's disease
Amyotrophic lateral sclerosis
Atherosclerotic cardiovascular disease
Benign prostatic hypertrophy
Chronic Obstructive Pulmonary Disease
Erectile Dysfunction
Infertility
Menopausal and perimenopausal disorders
Organic amnesic syndrome
(not caused by alcohol or other psychoactive substances)
Osteoarthritis
Parkinson's disease
Postmenopausal Osteoporosis
Vascular dementia/ Vascular cognitive disorder/impairment

Cancer:
- Basal cell
- Bladder
- Breast
- Cervical
- Colorectal
- Endometrial
- Gastric
- Hairy cell leukemia
- Lung (small & non-small cell)
- Multiple myeloma
- Oropharynx (squamous cell)
- Ovarian (non-germ cell)
- Pancreatic
- Prostate
- Renal cell
- Uterine

1.9.1 Request for Waiver of Pediatric Studies

The sponsor is requesting a waiver for the conduct of a clinical program with rivaroxaban for the prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) in pediatric patients (<18 years of age) undergoing total hip or knee replacement surgery. The rationale for the waiver for the conduct of such a clinical program in this indication is the rarity of joint replacement surgery in the pediatric population and the lower risk of DVT and PE (collectively referred to as venous thromboembolism [VTE]), which does not necessarily require routine prophylaxis.

Patients over 40 years old have a clearly increased risk for the development of VTE across multiple clinical settings compared with younger patients. The incidence of VTE in children is considered rare and usually happens only in the presence of a strong predisposing risk factor (Anderson 2003). However, even with a strong predisposing factor like major trauma, the incidence of clinically-detected VTE is lower in patients 17 years old or less compared with those over 17 years, based on a Level 1 trauma center registry (Azu 2005). VTE events were experienced in:

- 0 of 2320 (0.0%) trauma patients under the age of 13 years
- 2 of 1025 (0.2%) trauma patients between the ages of 13 to 17 years
- 57 of 10549 (0.5%) trauma patients older than 17 years

Based on these data, the authors concluded that VTE prophylaxis after trauma is unnecessary in children since the risk of clinically significant VTE is negligible. In adults, routine VTE prophylaxis after major trauma is a Grade 1A recommendation (Geerts 2008). Similarly, a review of all patients 17 years old or less hospitalized for at least 72 hours and having 2 or more risk factors for VTE, found only 1 case with symptomatic DVT (Rohrer 1996). Since this patient had at least 3 risk factors for VTE (i.e., head trauma, neurologic deficit, and multiple surgeries), the authors conclude that VTE prophylaxis is not required for patients with only 1 or 2 risk factors.

Total joint replacements are performed in the pediatric population primarily for the joint deformities and disabilities associated with juvenile rheumatoid arthritis (and similar conditions) (Kim 2008, Kitsoulis 2006). Since these procedures are technically challenging and will eventually lead to revision surgery due to the finite functional lifespan of the artificial joint, they are performed infrequently and only after medical therapy has failed. Joint replacement surgery is also occasionally performed in pediatric patients for malignant bone disease (e.g., with proximal femoral resection) (van Kampen 2008). Reflecting the low number of surgeries, the largest case series reported in the literature has been 47 patients from the Mayo Clinic (Klassen 1979). There does not appear to be any data in the literature on the occurrence of VTE following joint replacement surgery in pediatric patients, but based on the above data in other settings, the VTE risk would be expected to be substantially lower than for adults.

Since pediatric subjects were excluded from all rivaroxaban clinical studies and the risk of VTE is likely different from that in adults, the safety and effectiveness of rivaroxaban have not been established in children and adolescents <18 years of age and therefore, rivaroxaban is not recommended for use in this population in the proposed product labeling.

The conduct of a clinical program to establish the safety and effectiveness of rivaroxaban in the pediatric population after joint replacement surgery is not feasible due to the limited number of procedures performed and the low expected incidence of symptomatic VTE events in this population. Therefore, the sponsor requests a waiver for the conduct of such a clinical program.

References

Anderson FA, Spencer FA. Risk factors for venous thromboembolism. Circulation 2003;107;I-9-I-16. 5.4-1

Azu MC, McCormack JE, Scriven RJ, Brebbia J, Shapiro MJ, Lee TK. Venous thromboembolic events in pediatric trauma patients: is prophylaxis necessary? J Trauma Inj Infect Crit Care 2005;59:1345-1349. 5.4-1

Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicans evidence-based clinical practice guidelines (8th edition). Chest 2008;133:381S-453S. 5.4-1

Kim HJ, Kahn B, Figgie MP. Total joint replacement in childhood arthritis. Curr Rheumatol Rep 2008;10(2):135-41. 5.4-1

Kitsoulis PB, Stafilas KS, Siamopoulou A, Soucacos PN, Xenakis TA. Total hip arthroplasty in children with juvenile chronic arthritis: long-term results. J Pediatr Orthop 2006;26(1):8-12. 5.4-1

Klassen RA, Parlasca RJ, Bainco AJ. Total joint arthroplasty. Applications in children and adolescents. Mayo Clin Proc 1979;54(9):579-82. 5.4-1

Rohrer MJ, Cutler BS, MacDougall E, Herrmann JB, Anderson FA, Wheeler HB. A prospective study of the incidence of deep venous thrombosis in hospitalized children. J Vascular Surg 1996;24(1)46-9. 5.4-1

van Kampen M, Grimer RJ, Carter SR, Tillman RM, Abudu A. Replacement of the hip in children with a tumor in the proximal part of the femur. J Bone Joint Surg (American) 2008;90(4):785-95. 5.4-1

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because the necessary studies are impossible or highly impracticable. The conduct of a clinical program to establish the safety and effectiveness of Rivaroxaban in the pediatric population after joint replacement surgery is not feasible due to the limited number of procedures performed and the low expected incidence of symptomatic VTE events in this population.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Marcus Cato

3/13/2009 08:44:52 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: PEDIATRIC AND MATERNAL HEALTH STAFF (CDER/OND/PMHS)/ through Tammie Brent Howard,	FROM (*Name, Office/Division, and Phone Number of Requestor)*: Marcus Cato, RPM, Division of Medical Imaging and Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
March 10, 2009	N/A	22-406	Xarelto PI/Review	N/A

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xarelto™ (Rivaroxaban) Tablets	Rush	Factor Xa inhibitor	March 25, 2009

NAME OF FIRM: Johnson and Johnson (J&J)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

pregnancy portion of the PI (labeling)

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

DMIHP request PMHS to review and comment on the pregnancy portion of the proposed (labeling).

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Marcus Cato, RPM, Division of Medical Imaging and Hematology Products	☒ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

6. Reproductive and Developmental Toxicity

6.1 Study of Fertility and Early Embryonic Development in Rats after Oral Administration
(Study Number: T2062789)

Key findings: BAY-59-7939 at oral doses of 12.5 to 200 mg/kg/day in male and female rats during the fertility and reproductive performance period produced a reduction in number of dams (90.5%) with viable fetuses and a slight increase in post implantation loss. A dose related reduction in ovarian weight by 8.8% in the dams of the high dose group also occurred. The NOAEL was 50 mg/kg/day which provided 41 times the safety margin for the clinical dose.

Study no.: T2062789/AT01125/PH-33273
Conducting laboratory and location: The Department of Experimental Toxicology of BHC-PH-PD-T, 42096-Wuppertal, Germany.
Date of study initiation and completion: August 19, 2002 and April 7, 2004
GLP compliance: A statement of compliance was attached.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: J20020528, 9.5 % BAY 59-7939 coprecipitate; batch #F033082 and 99.3% pure, suspension made using 20 % Solution HS 15 and 80 % dermineralized water in addition with PEG 6000 according to the maximum PEG 6000 content of the high dose group formulation.

Methods
Doses: Male and female animals (12 week old; 24/sex/dose group) were randomly assigned to 4 groups using a randomization list by a computer program. BAY 59-7939 was administered by oral gavage, the intended route in humans in 10 ml/kg volume. Male rats were treated for 4 weeks prior to mating and during the subsequent mating period up to necropsy. Female rats were treated for 2 weeks prior to mating, during the mating period and to gestation day 7. The dose selection was based on a subacute toxicity study in rats (T7070622) and two kinetic studies with doses of 300 mg/kg and 400 mg/kg (T5068560 and T4062790). No meaningful higher exposure was achieved. The doses and the concentrations of the compound in each dose group are shown in sponsor's Table 7-2 of the submission:

Table 7-2

	Dose (mg/kg bw/day)	Test compound concentration (mg/ml)
Group 1 (Control)	0	0 (vehicle only)
Group 2	12.5	1.25
Group 3	50	5
Group 4	200	20

Species/strain: SPF-bred Wistar rats (strain: Hsd Cpb:WU), (b) (4)

Route, formulation, volume: Oral, suspension made using 20 % Solution HS 15 and 80 % demineralized water in addition with PEG 6000; 10 ml/kg.

Groups used for toxicokinetics: TK was not done

Parameters and endpoints evaluated: The general observations, appearance, behavior, excretion (feces and urine) and mortality were monitored twice daily during the pretreatment period (estrus determination days -6 to 0) in the female animals, during the entire treatment period in male and female animals. Females were observed up to the time of cesarean section (days 14 to 16 p.c.).

Body weight/Food Consumption: Body weights were taken twice a week during the entire treatment period in the male and female animals up to (and on) the day of necropsy. In inseminated females, daily body weight was monitored till the day of cesarean section. The food consumption changes were recorded during treatment up to the start of the mating period (weekly evaluation in males and females) as well as for inseminated females on day 0-7, and 7-14 p.c. The water consumption was estimated daily by visual examination of the water bottles.

Gross pathological examination: The animals were killed using deep carbon dioxide anesthesia and males were necropsied between study days 45 to 51 and, females on days 14 to 16 p.c. The gross examination of live and dead fetuses was done and, number of corpora lutea, implantation sites, resorptions, live and dead fetuses was counted and, placenta of each of the live and dead fetus was examined for gross changes. The reproductive organs (testes, epididymides, prostate, seminal vesicles, uterus, vagina, ovaries and pituitary gland) from all animals were separated, preserved in Davidson' solution (testes and epididymides) or in 10 % neutral buffered formalin solution. The implantation sites in non-pregnant animals without visible implantations were counted after staining with a solution of 10 % ammonium sulfide.

Results

Mortality: Four animals died and these were 2 males (1 of 50 and 200 mg/kg/day groups) were sacrificed in moribund condition on day 29 and day 18, respectively. Two females in 200 mg/kg/day treatment group died on premating day 10 and on gestation day 6. These animals showed sunken flanks, respiratory sounds, piloerection, and increased salivation after administration, and decreased water consumption. One male of control group also died on day 3. This animal showed hypoactivity, respiratory sounds, gasping breathing, reduced amount of feces, and salivation. The deaths were due to dosing errors.

Clinical signs: Increased incidence and duration of salivation in males of 50 and 200 mg/kg/day groups were noted.

Body weight changes: A reduction of 17.1% in the body weight gain was observed in females of 200 mg/kg/day group during treatment period and, 15.8% reduction was seen during gestation period. It was related to the reduction of food intake. The initial and final body weight of control females was 259 and 423 g.

Food and water consumptions: The food consumption of the 200 mg/kg/day treatment group males and females was significantly ($p<0.01$) less than the control from premating to mating and gestation periods. The food consumption in different study groups are shown in the sponsors table 8-1 and scanned below:

Table 8-1: Mean feed consumption (g/day) in the male animals during the premating period:

Dose (mg/kg bw/day)	week 1	week 2	week 3	week 4
0	29.14	28.12	27.03	27.08
12.5	28.98	26.95	26.70	27.55
50	28.04	27.61	27.43	27.67
200	24.99**	26.99	27.34	27.29

** significantly different from control, $p < 0.01$

Table 8-2: Mean feed consumption (g/day) in the female animals during the premating period and during gestation:

Dose (mg/kg bw/day)	week 1	week 2	days 0 – 7 p.c.	days 7 – 14 p.c.
0	17.11	17.67	21.41	23.55
12.5	16.89	16.95	21.18	25.10
50	16.33	17.20	20.39	22.97
200	14.90**	17.66	20.46	22.93

** significantly different from control, $p < 0.01$

There was no treatment related effects on water intake and excretory products in any animal of study dose groups among both genders.

Toxicokinetics: Not done

Necropsy:
One male of the 200 mg/kg/day group showed a treatment related black-brownish hematoma between testis and epididymides. No notable pathology was observed during necropsy in study dams included in the study.

Insemination Index, Fertility Index, Gestation Index

The insemination index, females with implantations, and with embryonic viability was similar in treated groups compared to controls. One of 21 females of high dose group was sacrificed because of moribund condition and another female showed reduced viable embryos. These females were excluded. The females with live embryos were 100, 100, 100 and 90.5% among 0, 12.5, 50 and 200 mg/kg/day groups, respectively, with viable embryos significantly less in the 200 mg/kg/day group. The data is shown in the following sponsor's table:

Table 8-6: Insemination index, fertility index and gestation index:

Dose (mg/kg bw/day)	used	inseminated n	inseminated % of those paired	with implantations n	with implantations % of those inseminated	with viable embryos n	with viable embryos % of those with implantations
0	23	22	95.7	19	86.4	19	100.0
12.5	24	24	100.0	20	83.3	20	100.0
50	24	24	100.0	21	87.5	21	100.0
200	23	23	100.0	21	91.3	19+	90.5

+ one female with sacrifice in moribund condition on day 6 p.c. was excluded

The mean number of estruses/female during 14 days of premating period were 2.9, 3.2, 3.5 and 3.3 in 0, 12.5, 50 and 200 mg/kg/day groups, respectively, therefore, treatment did not affect the number of estruses.

Cesarean Section Observations:

The number of corpora lutea, preimplantation and post implantation sites are shown in sponsor's table 8-9 and scanned here:

Table 8-9: Results obtained at cesarean section (mean values per female):

Dose (mg/kg bw/day)	0	12.5	50	200
Number of females	19	20	21	20
Corpora lutea	13.9	14.3	14.2	13.8
Implantations	11.5	13.0	12.4	11.9
Preimplantation loss	2.5	1.3	1.8	2.0
Postimplantation loss	0.2	0.4	0.7	0.8
Viable embryos	11.3	12.6	11.7	11.1

The mean number of corpora lutea was similar in treated animals compared to the control group animals.

Pre- and Post- implantation losses:
A dose related decrease in the mean number of post-implantation losses per female was observed in treated animals, i.e., number of late resorptions were 0.2, 0.4, 07 and 0.8 per female in study group animals The number of matings, fertility index and number of corpora lutea were similar in treated groups compared to control group females.

Weight of the Testes and Ovaries

The mean testicular and mean combined weights of the ovaries are given in the following table of sponsor and scanned below:

Table 8-5: Mean absolute combined testes and ovaries weights (g):

Dose (mg/kg bw/day)	0	12.5	50	200
Testes	3.693	3.701	3.647	3.710
Ovaries	0.114	0.106	0.106	0.104

BAY 59-7939 treatment up to 200 mg/kg/day produced a reduction in the mean ovarian weight (in comparison to control) of 5.3, 7.0 and 8.8% in females belonging to 0, 12.5, 50 and 200 mg/kg/day groups. The testes weight was not affected in males of the study.

In summary, BAY-59-7939 from the oral doses of 12.5 to 200 mg/kg/day in male and female rats during the fertility and reproductive performance period produced a reduction in number of dams (90.5%) with viable fetuses and a slight increase in post implantation loss and a dose related reduction in ovarian weight by 8.8% in the dams of the high dose group. The NOAEL was 50 mg/kg/day provides 41 times the safety ratio for the clinical dose.

B. **Study title: Developmental Toxicity Study in Rats after Oral Administration**
(Study #T3063590/PH-33582)

Key findings: BAY 59-7939 when administered in pregnant rats from 0, 10, 35 and 120 mg/kg/day doses from day 6 to 17 postcoitum produced dose related increase in plasma concentrations and vaginal bleeding, piloerection, hypo-activity and reduced feed intake. A severe body weight loss,

uterine bleeding, pale liver, kidneys and enlarged adrenal glands was reported in these animals. Dose related adverse effects of necrotic placental borders, necrotic, engorged and/or pale placentas were observed in fetuses of dams treated from 10 mg/kg/day or greater dose. BAY 59-7939 was not teratogenic in pregnant rats. Based on body surface exposure (mg/mm^3), it provides 97 times greater exposure than the proposed clinical dose.

Study no.: Study Number: T3063590/PH-33582

Conducting laboratory and location: Bayer HealthCare AG, PH-PD Toxicology International, Wuppertal (Germany)

Date of study initiation and completion: July 09, 2002 and November 18, 2004
GLP compliance: A statement of compliance with the OECD Principles of Good Laboratory Practice and with the revised German Principles of Good Laboratory Practice (German Chemicals Act (Bundesgesetzblatt Part I, No. 40, issued June 27, 2002) was attached.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: J20020528 – Coprecipitate 10%, 101

Methods

Doses Used: 0, 10, 35 and 120 mg/kg/day (vol = 10 ml/kg) once daily beginning from days 6 to 17 p.c.

Species/strain: The SPF-bred Wistar rats (strain – Hsd Cpb:WU, (b) (4) (b) (4)

Number/sex/group: 22 pregnant females/group

Route, formulation, volume, and infusion rate: Oral gavage suspension (prepared in demineralized water blended with PEG (polyethylene glycol) 6000, 10 ml/kg and the suspension made every two weeks.

Satellite groups used for toxicokinetics: 5 females/treated group treated and blood samples collected under light ether anesthesia on day 18 p.c. l, 3, 7, and 24 hours after administration. The animals were killed on day 18 p.c. and plasma samples stored deep frozen (< - 15°C) till sent for plasma concentrations.

Study design: Selected females were assigned to 4 treatment groups as shown below.

Table 5-1

	mg/kg body weight/day	concentration in mg/ml
Group 1 (Control)	0	0.0
Group 2 (Low dose)	10	1.0
Group 3 (Medium dose)	35	3.5
Group 4 (High dose)	120	12.0

On day 20 p.c., the general observations were recorded and the animals were c-sectioned and fetal intrauterine development was observed.

Clinical observations: All females of main study were examined twice/day excepting on weekends and holidays when examined once/day. The satellite groups were also examined twice/day and killed on days 18 p.c. (TK groups) and 20 p.c. (main groups). All findings related to changes in the general conditions of the rats and changes in feces and urine excretion were noted.

Body Weight & Feed and Water Intake of Females: Dams were weighed on day 0 p.c. and then daily from days 6 to 18 p.c. (satellite groups) or from days 6 to 20 p.c. (main groups). The corrected body weight gain calculated by subtracting the weight of the uterus on day 20 p.c. from the body weight gain over the period from day 0 to day 20 p.c. The food consumption was estimated for gestation days 0-3, 3-6, 6-9, 9-12, 12-1 5, 15-18, and 18-20 (in main groups). Water consumption was determined once daily by visual examination of remaining quantities of water in the bottles.

Toxicokinetic Investigations:
Venous blood samples were collected from study females of 10, 35 and 120 mg/kg/day satellite groups under light ether anesthesia on day 17 p.c. l, 3,7, and 24 hours after administration. The plasma from the blood samples and the samples were deep frozen (<-15°C) and sent for analysis and the toxicokinetic evaluations estimated.

Necropsy of Females:
On day 18 and 20 p.c., the satellite and main study group animals, respectively were subjected to cesarean section. The main study group uterine contents of females were examined for number of implantations (in females without visible implantation sites after staining of the uterus with a solution of 10 % ammonium sulfide). The uterus and placenta were weighed (individual weight and appearance), number of early resorptions (only implantation site visible) and late resorptions (fetal or placental remnant visible), and dead fetuses (fetuses without signs of life, but without maceration), number of live fetuses, fetal sex and their weights were taken.
External, visceral malformations and minor adverse abdominal, pelvic and thoracic organs abnormalities were evaluated in about half of the fetuses. The remaining half fetuses were used for skeletal abnormalities/ malformations after staining by the modified Dawson technique.

Results

Maternal observations:

Mortality: One female of 120 mg/kg/day dose group was sacrificed as it showed severe body weight loss, reddish vaginal discharge, piloerection, sunken flanks and hypoactivity. A reddish-brown fluid (blood) in the uterus and, pale liver, kidneys and enlarged pale adrenal glands was seen.

Clinical signs: Bloody vaginal discharge and piloerection were seen in 1 and all females belonging to 10 and 120 mg/kg/day groups, respectively. The bleeding in the 10 mg/kg/day group was claimed incidental since it was not present in 35/kg/day group dams. The treatment related effects in 120 mg/kg/day group were reduced food intake during treatment period (10.2, 16.0 and 24.8% on study days 9-12, 12-16 and 15-18 p.c, respectively), and water intake and reduced fecal contents. On necropsy of these animals, an enlarged spleen and pale liver were seen in 1 female of 120 mg/kg/day group.

Toxicokinetics: Rat plasma concentrations of blood samples collected after 1, 3, 7 and 24 h of the dosing were determined on day 17 post coiturn (p.c.). AUC (0-24) was increased in a treatment

related manner. The peak concentration reached in about 1-3 hours. The ratio of the trough to peak concentration increased markedly from 0.7 to 5.7 and 29.2% with increasing doses (saturated and/or protracted absorption) as shown in the table below.

Dose [mg/kg]		10	35	120
AUC(0-24)	[mg·h/L]	18.9	77.7	188
$AUC(0-24)_{norm}$	[kg·h/L]	1.89	2.22	1.57
C_{max}	[mg/L]	2.55	6.59	12.9
$C_{max,norm}$	[kg/L]	0.255	0.188	0.108
$C(24)/C_{max}$	[%]	0.713	5.70	29.2
t_{max}	[h]	3.00	3.48	2.08

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Embryo-Fetal Survival, Fetal Weight and Gravid Uterine Weight: The mean number of implantations, numbers of corpora lutea, preimplantation losses and implantation sites in the treatment group females were similar to control group animals (shown in sponsor's table 6-3).

Table 6-3

Dose [mg/kg bw/day]	0	10	35	120
inseminated females	22	22	22	22
inseminated females evaluated	22	22	22	22
females with implantations	19	22	20	19[1]
in % of those inseminated	86.4	100.0	90.9	90.5
mean values per female with implantation sites				
corpora lutea	12.5	13.5	13.1	13.5
preimplantation loss	0.9	1.2	1.6	0.8
implantations	11.6	12.3	11.6	12.7

[1] one female with implantation sites was sacrificed in moribund condition on day 16 p.c.; excluded from calculations

Effect of Test Compound on Intrauterine Development

Gestation Rate

The gestation rate (number of females with viable fetuses as a percentage of the number of females with implantations) was not affected by up to the high dose of 120 mg/kg/day BAY 59-7939 (see Table 6-4 below)

Table 6-4

Dose [mg/kg bw/day]	Females with viable fetuses N	Females with viable fetuses in % of females with implantations	Females with total resorption
0	19	100.0	0
10	22	100.0	0
35	20	100.0	0
120	19	100.0	0

The mean values for the parameters of intrauterine development were unaffected by up to 120 mg/kg/day BAY 59-7939 treatment groups (shown below in sponsor table 6-5).

Table 6-5

Dose [mg/kg bw/day]	0	10	35	120
number of females				
with implantations (a)	19	22	20	19
with viable fetuses (b)	19	22	20	19
means per female				
placental weight in g (b)	0.65	0.62	0.67	0.61
number of live fetuses (b)	11.2	11.3	10.9	12.1
postimplantation loss (a/b)	0.4	1.0	0.7	0.6
% males (b)	56.6	48.7	50.1	43.2
fetal weight in g (b)	3.59	3.57	3.70	3.48

Statistically significant increase in incidences of necrotic placental borders in animals of 10, 35 and 120 mg/kg/day groups were seen. An increased number of engorged placentas and, pale colored and necrotic placentas were found in 120 mg/kg/day group animals. The mean placental weight was not affected in 120 mg/kg/day group.

Postimplantation Loss, Number & sex of Fetuses

One female of 10 mg/kg/day group had reddish vaginal discharge and late resorptions of 5 of 10 implantation sites at the cesarean section time and no postimplantation loss in 120 mg/kg/day group. Mean litter size was in the treated groups were not different from control group. The mean percentage of male fetuses/litter was slightly low (43.2%) in 120 mg/kg/day group.

Fetal Observations:

Mean fetal weights were 3.598, 3.578, 3.70 and 3.48 g and, mean litter size were 11.2, 11.3, 10.9, and 12.1 in the 0, 10, 35 and 120 mg/kg/day groups, respectively. There were no treatment or dose related external, skeletal and visceral malformations among viable fetuses up to 120 mg/kg/day treatment group.

Fetal External and Visceral Deviations

No external and visceral deviations (findings other than malformations) in live fetuses (%) or litters were detected. A treatment-related effect for the occurrence the incidence of hemorrhages at different organs (mandible, thyroid, pericardium, abdominal cavity and liver) was seen. These findings were not dose dependent and were in the range of historical control data of sponsor submitted with the document. BAY 59-7939 administered during the period of organogenesis in pregnant rats caused no developmental abnormalities and was not teratogenic. Based on body surface exposure (mg/mm^3), it provides 97 times greater exposure than the proposed clinical dose.

C. **Study title: BAY 59-7939 Developmental Toxicity Study in Rabbits after Oral Administration** (Study # TO062930/PH-33380/AT01303)

Key findings: Orally administered BAY 59-7939 produced a linear increase in systemic exposure in 0.5 to 2 h on day 20 p.c. The treatment produced an increased incidence in cold ears at all dose levels. The treatment with BAY 59-7939 produced abortions at all doses and doses of 40 and 160 mg/kg/day were maternally lethal. Treatment related

external and visceral deviations or malformations were not seen up to 160 mg/kg/day. BAY 59-7939 was not teratogenic in rabbits of the study. Systemic maternal NOEL and intrauterine development safe dose was 2.5 mg/kg/day in the study and provides 4 times greater exposure in the study animals.

Study no.: TO062930/PH33380/AT-01303
Conducting laboratory and location: BHC-PH-PD Toxicology International, Bayer HealthCare AG, 42096 Wuppatal, Germany.
Date of study initiation and Completion: June 12, 2002 and July 6, 2004
GLP compliance: A statement that the study was conducted in compliance with ICH guideline "Detection of Toxicity to Reproduction for Medicinal Products" (EU 1993, Japan MHLW 1994, US-FDA 1994).
QA reports: yes (X) no ( )
Drug, lot #, and % purity: J20020430, 9.5 % BAY 59-7939

Methods
Animal, Strain: Twenty female Himalayan rabbits/group (between 120 and 274 days old) weights ranged from 2104 to 3361 g on day 0 p.c.
Doses: i. Main study group: 0, 2.5, 10, 40, and 160 mg/kg/day BAY 59-7939 Coprecipitate l0 % l00 in demineralized water.
ii. Toxicokinetics group: 3/sex/group animals
The daily oral dose was administered (gavage) as in addition with PEG 6000 from days 6 to 20 p.c. as shown following table (sponsor's table):

Table 7-1

	mg/kg body weight/day	concentration in mg/ml
Group 1 (Control)	0	0
Group 2 (Additional low dose)	2.5	0.5
Group 3 (Low dose)	10	2
Group 4 (Medium dose)	40	8
Group 5 (High dose)	160	32

The dose selection was based on a pilot developmental toxicity study in pregnant rabbits (study #T1071003) with 0, 10, 30, 100 and 200 mg/kg/day (dose volume 5 ml/kg) BAY 59-7939 Coprecipitate 10 % 100 from day 6 to day 20 p.c. One animal of 200 mg/kg/day had reduced gestation rate and aborted on day 20 p.c. Body weight loss was seen in all treatment group animals and necropsy showed an enlarged caecum. The dose of 100 mg/kg/day produced post implantation loss and decreased fetal weights. The dose between 100 and 200 mg/kg/day was identified as the high dose for the present study and sponsor selected 160 mg/kg/day as the high dose in the present study.

Parameters Evaluated:
Clinical observations: All females of main study were examined twice/day from days 0-29 p.c. and satellite group from days 0-21. All findings related to changes in the general conditions of the rabbits (appearance, behavior) and changes in amounts of feces and urine excretion were noted.

Body Weight & Feed and Water Intake of Females: The animals were weighed on day 0 p.c. and daily from days 6 to 21 p.c. (satellite groups) or from days 6 to 29 p.c. (main groups). The food consumption was estimated for gestation Days 0-3, 3 - 6, 6 -9, 9-12, 12-15, 15-18, 18-20, 20-21, 21-24, 24-27, and 27-29 p.c. for the main groups, and days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-20, and 20 -2 1 p.c. for the satellite groups. Water consumption was determined once daily by visual examination of remaining quantities of water in the bottles.

Toxicokinetic Investigations:
Venous blood samples were collected from study females of 2.5, 10 and 40 mg/kg/day satellite groups under light ether anesthesia on day 6 and 20 p.c. at 0.5, l, 2, 4, 6 and 24 hours after administration. Venous blood samples (extremity veins) were collected from three females of the 160 mg/kg/day main group on day 20 p.c. at 30 minutes as well as 1, 2, 4, 6, and 24 h after administration, because three females were replaced in satellite group. The plasma samples were deep frozen (< - 15°C) and sent for analysis and the toxicokinetic evaluations.

Necropsy of Females:
The females of main and satellite group were dissected on day 29 and 21 p.c., respectively, and uterine contents examined for number of implantations (in females without visible implantation sites after staining of the uterus with a solution of 10 % ammonium sulfide). The uterus and placenta were weighed (individual weight and appearance), number of early (only implantation site visible) and late resorptions (fetal or placental remnant visible), and dead fetuses (fetuses without signs of life, but without maceration), number of live fetuses, fetal sex and their weights were determined. External, visceral malformations and minor adverse abdominal, pelvic and thoracic organs abnormalities were evaluated in about half of the fetuses. The remaining half fetuses were used for skeletal abnormalities/ malformations after staining by the modified Dawson technique.

Results:

A. Maternal Dam Data:
The treatment related incidences of cold ears were increased in 11, 23, 15, and 23 animals in the 0, 2.5, 10, 40 and 160 mg/kg/day groups, respectively, from day 6 p.c. Daily water intake and urine excretion were decreased in animals of 40 and 160 mg/kg/day treatment groups

Mortality: Two of 24 females in each of 40 and 160 mg/kg/day groups were found dead.

Body Weight and Food consumption Changes:
A severe reduction in the body weight gain in animals of 10, 40 and 160 mg/kg/day groups was seen from days 6-20 p.c. as shown below in the Table 8-2.

Table 8-2

Dose (mg/kg b.w./day)	0	2.5	10	40	160
absolute body weight gain (g) days 6 - 20 p.c.					
	46.5	102.1	29.1	9.9	11.8
absolute body weight gain (g) days 0 - 29 p.c.					
	206.6	316.6	151.6	157.2	144.2
corrected body weight gain (g) days 0 - 29 p.c.					
	- 146.0	- 62.3	- 197.7	- 168.3	- 119.7

Fetal Observations & Evaluation:
A marginal reduction was seen in the gestation rate in the 2.5 mg/kg/day group and, total resorption was seen in 1, 1, 2 and 2 females of the 2.5, 10, 40 and 160 mg/kg/day groups, respectively, on days 1 8 to 26 p.c. One, 2 and 2 females in each of 10, 40 and 160 mg/kg/day groups, respectively, aborted between day 18 and 26 p.c. The females that aborted or all females in these groups showed decrease in feed intakes and body weight loss since beginning of treatment on day 6 p.c. The females which had total resorptions showed slight to marked body weight loss during treatment (-40 g to -194 g), cold ears, and reddish excretion.

Gross Pathology Changes**:**
Enlarged and gaseous contents in caecum was observed in 4 and 1 females of the 40 and 160 mg/kg/day groups, respectively and only enlarged caecum was in females of the 2.5 and 10 mg/kg/day groups. Pale liver, enlarged gall bladder, hardened fatty tissue, mottled and smaller in size spleen, and pale kidneys were the other observation in the 160 mg/kg/day group.

General Reproduction Data:
The fertility data including mated females and, number of implantations, corpora lutea and preimplantation losses were similar in treatment group animals compared to the control group animals (as shown in the following table scanned from sponsor's submission). Three and 2 females of 40 and 160 mg/kg/day groups, respectively, were withdrawn and excluded from the study.

Table 8-3

Dose (mg/kg b.w./day)	0	2.5	10	40	160
mated females	20	20	20	20	12
mated females evaluated	20	20	20	18[+]	9[++]
females with implantations	20	20	20	18	9
in % of those mated	100.0	100.0	100.0	100.0	100.0
mean values (without females displaying abortions) per female with implantation sites					
corpora lutea	8.0	8.3	7.5	8.0	8.9
preimplantation loss	1.4	0.9	0.5	1.0	1.1
implantations	6.7	7.3	7.0	7.0	7.7

\+ two females with death were excluded
++ two females with death were excluded, and one female was excluded due to withdrawal of this dose group

The total resorption was observed in each dose group animals of 2.5, 10, 40 and 160 mg/kg/day and, 1, 2 and 2 females of 10, 40 and 160 mg/kg/day groups aborted. Thus, BAY 59-7939 treatment produced abortions in rabbits from 10 mg/kg/day dose. This should be described in the label. Additionally, increased incidences of coarse grained placentas were noted at l0 mg/kg/day and above study doses.

Table 8-4

Dose	Females with			
	viable fetuses on day 29 p.c.		abortion	total resorption
mg/kg b.w./day	n	in % of females with implantations	n	n
0	20	100.0	0	0
2.5	19	95.0	0	1
10	18	90.0	1	1
40	15	83.3	2	1
160	6	66.7	2	1

Appearance and Weight of Placentas

The increased incidences of course/rough grained placentas were from the 10 mg/kg/day and higher dose treatment groups. Significant increased number of necrotic placentas was reported in 40 and 160 mg/kg/day group animals. The placental weights were decreased in females of 40 and 160 mg/kg/day groups. Therefore, the low dose 10 mg/kg/day produced the changes in external appearance of placentas and increased incidence of coarse grained placentas.

Postimplantation Loss, Number of Fetuses

There was an increase in the mean postimplantation loss in females with viable fetuses at cesarean section in 10, 40 and 160 mg/kg/day treated groups but a statistical significant increase was found in 160 mg/kg/day group animals. The numbers of late resorptions were the consequence of the increased postimplantation loss. The mean number of fetuses was slightly decreased in the 160 mg/kg/day group.

Sex/Weight of Fetuses:

BAY 59-7939 treatment affected the fetal growth and the fetuses from 40 and 160 mg/kg/day treatment groups dams weighed significantly lesser than controls (lower range of sponsor's historical control data). Thus, the fetal growth was affected from 40 mg/kg (slightly) group and the NOAELwas 10 mg/kg/day.

Fetal Malformations:

The treatment with the compound during organogenesis did not produce external and visceral deviations up to 160 mg/kg/day. The retardation of the vertebral ossifications and infusion of sternebrae (variation) was reported in 40 and 160 mg/kg/day groups. The total numbers of fetuses or litters with malformations was not increased in a dose related manner up to 40 mg/kg/day group. The incidence of fused caudal certebral bodies at the 40 mg/kg dose were above the historical control data (up to 2.02 %). The incidences of major ventricular septal defect of the heart with/without enlarged pulmonary artery was found in 1 litter of 160 mg/kg/kg/day group, that was 6.6 % and it was greater than the incidences of up to 1.85 % in historical control data.

Toxicokinetics:

Plasma concentrations of BAY 59-7939 were determined after oral administration to pregnant rabbits on day 6 and day 20 p.c. Blood samples were collected at 0.5, 1, 2, 4, 7 and 24 h after administration. The exposure on day 20 (means, n = 3) was as follows:

		Dose [mg/kg]			
		2.5	10	40	160*
AUC(0-24)	[mg·h/L]	0.736	2.78	13.1	23.9
$AUC(0\text{-}24)_{norm}$	[kg·h/L]	0.294	0.278	0.329	0.150
C_{max}	[mg/L]	0.142	0.294	0.881	1.54
$C_{max,norm}$	[kg/L]	0.0568	0.0294	0.0220	0.00964
$C(24)/C_{max}$	[%]	5.36	12.3	46.2	59.2
t_{max}	[h]	0.794	2.00	1.00	1.00
R_{A1}	[%]	79.1	66.4	68.7	n.c.
R_{A2}	[%]	n.c.	328	283	n.c.
R_{A3}	[%]	105	128	132	n.c.

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n.c. = not calculated
* = data for this dose group only available from Day 20
$R_{A1} = C_{max,Day\ 20} / C_{max,Day\ 6}$
$R_{A2} = C_{(24),Day\ 20} / C_{(24),Day\ 6}$
$R_{A3} = AUC_{(0\text{-}24),Day\ 20} / AUC_{(0\text{-}24),Day\ 6}$

On day 20 p.c., a linear increase in systemic exposure ($AUC_{0\text{-}24hr}$) was seen in study animals. The maximum concentrations were observed around 0.5 to 2 h on day 20 p.c. Data from the 160 mg/kg/day dose group were only available on day 20 p.c.

In summary, BAY 59-7939 administration produced a linear increase in rabbit plasma concentration ($AUC_{0\text{-}24hr}$) in 0.5 to 2 h on day 20 p.c. Increased incidences of abortions were observed at all dose levels. The doses of 40 and 160 mg/kg/day were maternally lethal. Treatment related external and visceral deviations or malformations were not seen up to 160 mg/kg/day. BAY 59-7939 was not teratogenic in rabbits of the study. Systemic maternal NOEL and intrauterine development safe dose was 2.5 mg/kg/day in the study and provides an exposure which was 4 times the exposure of human dose.

D. **Study for Effects on Pre- and Postnatal Development in Rats Including Maternal Function after Oral Administration (**Study No. : T9062957)

Key study findings: Wistar rats were treated BAY 59-7939 Coprecipitate 10 % 100 at oral gavage doses of 0, 2.5, 10, and 40 mg/kg/day in pregnant females produced overt pharmacologic effect of generalized tissue bleeding in 10 and 40 mg/kg/day treatment group animals and the 40 mg/kg/day dose was maternally lethal. Still birth and empty stomach/intestines were observed in pups born to 10 and 40 mg/kg/day treated groups dams. The postnatal developmental adverse effects observed in pups were hypoactivity, pale skin, cold to touch surface, and not detectable milk spots. The identified NOAEL for maternal effects (F0) and, pre- and postnatal development of the F1 generation was 2.5 mg/kg/day and provides 4 fold safety margin for the proposed human dose).

Study no.: T9062957/PH34608
Conducting laboratory and location:
Date of study initiation & completion: January 14, 2004 & September 27, 2006
GLP compliance: The study was conducted in compliance with ICH guideline "Detection of Toxicity to Reproduction for Medicinal Products" (EU 1993, Japan MHLW 1994, US-FDA 1994).
QA reports: yes (X) no ( )
Drug, lot #, and % purity: #030723-100 BAY 59-7939 Coprecipitate 10 % 100

Methods

Doses: 0, 2.5, 10, and 40 mg/kg/day BAY 59-7939 Coprecipitate 10 % 100 formulated in 20 % Solutol HS 15 and 80 % demineralized water in addition with PEG 6000 (volume = l0 ml/kg)

Species/strain: SPF-bred Wistar rats (strain Hsd Cpb:WU)

Number/sex/group: **F0** - 25/inseminated females/group; **F1** - one male and one female per litter/study treatment group to test the fertility of the F1 generation

Route, formulation, volume: Oral gavage

Study design: The dams treated by oral gavage once daily on Day 6 pc through Day 20 pp with an aim to determine the effects of BAY 59-7939 on pregnancy, parturition, lactation and on pre- and postnatal survival and also on neurobehavioral growth and, the development of reproductive parameters of F1 and F2 generations. The females were allowed to deliver and rear their offspring up to day 21 p.p. During, at the end or after the rearing period the physical and functional development of the F1 pups was monitored. One F1 female/litter were reared up to maturity for reproductive and fertility testing.

Postweaning Evaluations

F1 Pups were tested for auditory startle reflex (postnatal day 27 to 31), passive avoidance test for learning/retention once between postnatal Day 40 and 50 using an automated system and, motor activity (postnatal day 54 to 61).

Fertility, Reproductive performance and parturition observations of F1 rats:
The estrous cycle of F1 females was determined from postnatal day 64 to 73 (beginning on postnatal day 73 to 80) until mated. Mated females (F1) were allowed to deliver their F2 litters. The dams were weighed on day 0, 7, 14 and 21 pc and day 1 and 7 pp and, checked frequently between 0800 and 1800 hours to record the date and time of parturition. Number of pups, the day parturition (pp day 0) were noted and pups counted and weighed on day 0, 7, 14 and 21 pc and day 1 and 7 pp. The test to determine 'stillborn'/'born alive' pup was performed. F1 females were euthanized on post natal 23 and uterine contents examined for implantations (stained with ammonium sulfide if apparently not pregnant), resorptions and live and dead fetuses were counted.

F2 pup evaluations and termination: The pups were examined by general observation, number, weights and sex determined. The pups were weighed on postnatal days 1 and post-partum day 7. The cause of death (still born/born dead) of F2 was determined and surviving F2 pups were euthanized by carbon dioxide asphyxiation on Day 7 pp and discarded.

Results:

F_0 Dams:

General Observations: The fertility index of study groups F0 dams up to 40 mg/kg/day was comparable to control and in the range of historical control data. But the rearing index of dams treated with 40 mg/kg/day group was decreased. The gross necropsy in one 40 mg/kg/day female revealed a cervix tightly filled with greenish muddy fluid and 14 dead fetuses in the

uterus. An additional female of 40 mg/kg/day group showed a preterm delivery and all pups died. In 40 mg/kg/day group females, treatment related hypoactivity, high stepping gait, piloerection, cold skin, pale eyes, and salivation were noted. Increased incidences of light colored feces during gestation (0-21 p.c.) period were reported. During the lactation period, discolored feces were seen in 10 and 40 mg/kg/day groups.

Mortality: Seven of 25 females of 40 mg/kg/day group were sacrificed in moribund condition. Salivation, hypoactivity, high stepping gait, piloerection, cold skin, reddish vaginal discharge, preterm delivery (female no. 51, only), pale eyes, and salivation were observed. Gross necropsy of the dams showed a pale liver and spleen. All of the pups of these animals died.

Body weight/Food consumption: A 16.8% reduction in the body weight was reported in the females of 40 mg/kg/day treatment group during the treatment period between days 6-20 p.c. The body weight reduction was 20.6% during the gestation period (days 0-20 p.c.). The food consumption was reduced significantly in animals of 40 mg/kg/day group as shown below in the table:

Table 6-1: Mean Feed Intake of the F0 Females

Dose [mg/kg bw/day]	0	2.5	10	40
Mean feed consumption during gestation [g/female/day]				
days 0 - 6 p.c.	21.4	21.0	21.5	21.0
days 6 - 11 p.c.	21.7	21.7	22.1	19.9*
days 11 - 16 p.c.	23.2	23.1	23.2	21.0**
days 16 - 20 p.c.	26.6	25.4	26.1	20.9**
Mean feed consumption during lactation [g/female/day]				
days 0 - 7 p.p.	42.4	40.5	41.6	40.1
days 7 - 14 p.p.	65.5	62.3	61.7	61.6

Statistically significant difference to control * = $p < 0.05$
Statistically significant difference to control ** = $p < 0.01$

C-Section Observations of (F0) rats: Placentas with greenish/yellowish borders were seen and dark red mass (clotted blood) most likely due to an impaired delivery in lung and heart was reported in pups born to 40 mg/kg/day treatment group animals. A treatment related enlarged spleen was noted in two females of the 10 mg/kg/day.

Table 6-3: Fertility, Gestation, and Rearing Indices of the F0 Females

Dose	females used	Fertility index females with implantations		Gestation index females which delivered		Rearing index females which reared pups	
[mg/kg bw/day]	n	n	% of those used	n	% of those with implantations	n	% of those which delivered
0	25	19	76.0	18	94.7	18	100.0
2.5	25	21	84.0	21	100.0	21	100.0
10	25	23	92.0	23	100.0	23	100.0
40	25	24	96.0	22	91.7	17	77.3

The gestation index was similar in treated and control group animals but the rearing index was decreased at the 40 mg/kg/day group. Gestation period was unaffected by BAY 59-7939 but impaired delivery was noted in 2 of 24 females of the 40 mg/kg/day group. One of these animals was killed in moribund condition and the other animal had a preterm delivery and all pups died thereafter. The viability index (up to day 4 p.p.) was

statistically significantly decreased in pups of 40 mg/kg doses. The lactation index (up to day 21 p.p.) was unaffected by treatment up to 40 mg/kg.

F1 Generation Physical & Behavioral Development Evaluation:
A statistically significant increase in pup mortality (including pups found dead, missing, sacrificed in moribund condition, and cannibalized) occurred at the 40 mg/kg level from days 0-4 p.p. Increased incidences of hypoactivity, pale skin, cold to touch surface in 40 mg/kg/day group pups was reported. An increased incidence of pale skin was also seen in pups of 10 mg/kg/day group. At necropsy on day 42 p.p. a treatment related pale liver and increased incidences of pups with no milk spots of 40 mg/kg group animals was reported. The reflex and behavioral tests showed adverse toxic effects on sucking reflexes of pups in 40 mg/kg/day group and no effect on sensory functions up to 40 mg/kg/day dose. The necropsy data of F1 pups is shown in the following table (sponsor's table on page 121 of eTCD). On day 42 p.p., an increase in the incidences of pups with empty stomach and intestines at 40 mg/kg/day and, stillborn pups occurred at 10 mg/kg/day or higher dose.

T9062957 BAY 59-7939

(F0 GENERATION)
SUMMARY OF PUP NECROPSY OBSERVATIONS

		0 MG/KG	2.5 MG/KG	10 MG/KG	40 MG/KG
Litters Evaluated	N	18	21	23	21
Pups Evaluated	N	167	195	199	168
Live	N	167	195	199	168
Stillborn	N	0	0	0	0
LIVER					
LIVER PALE					
Pup Incidence	N	0 f	0	0	1
	%	0.0	0.0	0.0	0.6
	p-value	0.342			
Litter Incidence	N	0 f	0	0	1
	%	0.0	0.0	0.0	4.8
	p-value	0.393			
Affected Pups/Litter	MEAN%	0.00 k	0.00	0.00	0.68
	S.D.	0.000	0.000	0.000	3.117
	p-value	0.399			
LIVER BLACKISH DISCOLORED					
Pup Incidence	N	0 f	2	4	3
	%	0.0	1.0	2.0	1.8
	p-value	0.313			
Litter Incidence	N	0 f	1	2	1
	%	0.0	4.8	8.7	4.8
	p-value	0.645			
Affected Pups/Litter	MEAN%	0.00 k	0.79	1.93	2.04
	S.D.	0.000	3.637	7.226	9.352
	p-value	0.658			
STOMACH					
STOMACH EMPTY					
Pup Incidence	N	0 f	0	0	16**
	%	0.0	0.0	0.0	9.5
	p-value	0.000			0.000
Litter Incidence	N	0 f	0	0	2
	%	0.0	0.0	0.0	9.5
	p-value	0.109			
Affected Pups/Litter	MEAN%	0.00 k	0.00	0.00	7.01
	S.D.	0.000	0.000	0.000	22.866
	p-value	0.113			

Statistical key: f=Fisher's Exact k=Kruskal-Wallis ** = p<0.01

The clinical findings of head tilted, respiratory sounds, piloerection, wound, hematoma, blackish discolored or missing tip of tail, tail bent, restricted motility of right forelimb)

were observed in all treated group pups. One pup with tilted neck was also seen in the control group. Increased pup mortality occurred in 40 mg/kg/day treated dams in the study.

F1 Generation Fertility & Reproductive Development Evaluation

The feed and water consumption, excretions, body weights of the F1 generation after weaning, and gross pathological findings showed no treatment related effects in F1 males and females up to 40 mg/kg/day dose. The insemination, fertility, and gestation indices of the F1 generation as well as time to insemination, number of implantation sites, duration of gestation, litter size (number of viable pups) and number of stillborn pups, sex ratio of F2 pups, clinical findings including malformations, and body weights of the F2 pups were also unaffected by treatment with BAY 59-7939 at doses up to and including 40 mg/kg. But an increased incidence of stillborn F2 pups and a slightly increased incidence of pups with pale skin occurred at the 10 and 40 mg/kg/day group. An increased % mortality occurred among F2 of 40 mg/kg/day group from days 0-4 p.p. The other effects of increased incidences of pups with hypoactivity, pale skin, cold to touch surface, and not detectable milk spots were also seen in these pups.

The number of viable pups/litter were similar between the control and was marginally decreased in 10 and 40 mg/kg/day groups due to the increased number of stillborn and deaths of pups in 40 mg/kg/day group. After litter reduction on day 4 p.p. a treatment related effect on litter size was not seen up to 40 mg/kg/day. The litter size of F1 generation is shown below:

Table 6-8: Mean Litter Sizes of the F1 Generation

Dose [mg/kg bw/day]	0	2.5	10	40
Day p.p.	Number of viable pups (mean values, male and female pups combined)			
0	12.39	11.71	10.91	11.00
4 before reduction	11.83	11.62	10.48	10.59
4 after reduction	7.94	7.67	7.52	7.53
7	7.94	7.67	7.52	7.47
14	7.94	7.57	7.48	7.41
21	7.94	7.52	7.39	7.41

The lactation index (up to day 21 p.p.), sex ratio, mean body weight of F1 Pups during of rearing was similar in treated group animals compared to controls.

Table 6-12: Physical Development of the F1 Pups

	Dose [mg/kg bw/day]			
	0	2.5	10	40
Parameter of physical development	Days after birth			
Pinnae detachment	2.28	2.44	2.24	2.28
Development of fur	9.49	9.47	9.72	9.50
Incisor eruption	9.48	9.62	9.60	9.50
Eyes opened	16.32	16.40	16.50	16.10
Normal gait	16.61	16.63	16.93	16.37
Balanopreputial separation	46.0	46.0	46.7	46.1
Body weight at balanopreputial separation [g]	219.8	223.5	230.2	215.2
Vaginal opening	32.8	33.2	33.2	33.5
Body weight at vaginal opening [g]	103.5	106.9	107.9	106.5

Reflex and Behavioral Tests on the F1 Pups Reflex Testing

The surface righting reflex, negative geotaxis, hearing test and pupillary reflex tests showed no relevant drug related aberration/change in these tests.

Table 6-13: Reflex Tests of the F1 Pups

	Dose [mg/kg bw/day]			
	0	2.5	10	40
	Tests for reflexes and sensory functions			
Surface righting (days p.p.)	1.03	1.03	1.04	1.02
Negative geotaxis (days p.p.)	5.15	5.13	5.14	5.04
Hearing test (positive in %)	100.00	100.00	100.00	100.00
Pupillary reflex (positive in %)	100.00	100.00	100.00	100.00

Motor Activity & Water-M-Maze Testing

The results of the motor activity testing with the F1 animals showed no treatment related difference between control and treatment group F2 animals. No treatment related adverse development motor effects were seen in F2 pups.

Table 6-13: Reflex Tests of the F1 Pups

	Dose [mg/kg bw/day]			
	0	2.5	10	40
	Tests for reflexes and sensory functions			
Surface righting (days p.p.)	1.03	1.03	1.04	1.02
Negative geotaxis (days p.p.)	5.15	5.13	5.14	5.04
Hearing test (positive in %)	100.00	100.00	100.00	100.00
Pupillary reflex (positive in %)	100.00	100.00	100.00	100.00

Gross Pathological Findings in the F1 Pups up to the End of Rearing

The gross pathological necropsy findings of the F1 pups up to day 42 p.p. were autolytic pups, reduced eye ball size or missing, spleen blackish discolored, liver yellowish or blackish discolored, stomach distended or tightly filled with feed paste, dilation of renal pelvis, contents of intestines blackish discolored, testes missing or reduced in size, abdominal cavity contains dark red to blackish mass, and shortening of skull bones after skeletal staining. A significantly increased incidences of pups with empty stomach and intestines was observed in animals included in the 40 mg/kg/day group.

Pre- and postnatal Development

The gestation duration and index in the treated and control group was unaffected by 40 mg/kg/day BAY 59-7939. The rearing index was slightly decreased at the 40 mg/kg/day dose level. The parturition was affected in two females of the 40 mg/kg group which were sacrificed in moribund condition and these had impaired delivery. One female of 40 mg/kg/day group had a preterm delivery with all pups died. Increased incidences of pups without milk spots and stillborn pups and, an increased incidence of pups with pale skin occurred at the 10 mg/kg/day dose level, for which a treatment related effect cannot be excluded. Increased pup mortality occurred at the 40 mg/kg/day group from days 0-4 p.p. together with increased incidences of pups with hypoactivity, pale skin, cold to touch surface, and not detectable milk spots. The increased pup mortality was in a dose related manner during the study. There was decreased number of viable pups/litter in dams of 10 and 40 mg/kg/day groups. An increased number of stillborn pups were born to 40 mg/kg/day group dams. A treatment related increased incidence of empty stomach and intestines was noted in pups born to 40 mg/kg treated dams and these showed pale liver which suggested possible liver toxicity. Thus, treatment increased the incidences of developmental adverse effect on sucking reflex in pups.

Development of the F1 Generation after Weaning:

Appearance, Behavior, and Mortality:
One female and 1 male of 2.5 and 40 mg/kg/day groups were killed on day 108 p.p. and day 0 after delivery. Treatment related effects on feed and water consumption were not evident in males and females of the F1 generation up to 40 mg/kg/day group. Fecal and urine excretion were not affected by the compound.

Gross Pathological Findings
One F1 male had a left testis lying in a pocket of the abdominal wall, and an additional F1 male of the 40 mg/kg dose group had dilation of the right renal pelvis. The incidence was within the historical data sent by sponsor. Thus, no treatment related gross pathological findings occurred in the F1 males and females. No treatment related change in the mean values for feed consumption during premating and gestation (females, only) period was seen.

Fertility Testing of F1 Generation (Insemination, Fertility, and Gestation Indices):
The insemination index [% = Number of females inseminated x 100 ÷ Number of females paired] were similar in the treated and control group animals and shown below.

Table 6-15: Insemination, Fertility, and Gestation Indices of the F1 Females

	Number of F1 Females						
Dose [mg/kg bw/day]	Used [n]	Inseminated [n]	% of those mated	with I.S. [n]	% of those inseminated	which delivered [n]	% of those with I.S. / used
0	24	23	95.8	19	82.6	19	100.0
2.5	24	24	100.0	23	95.8	22	95.7
10	24	23	95.8	21	91.3	21	100.0
40	24	24	100.0	23	95.8	23	100.0

I.S. = implantation sites

The insemination, fertility and gestation days were not affected in F1 generation rats. The time of insemination in the pups of treated dams showed that the insemination rate and other fertility data in treated and control dams were similar.

Table 6-17: Mean Values of the Parameters of Intrauterine Development of the F1 Females, Weights and Sex ratio of F2 Pups

Dose [mg/kg bw/day]	0	2.5	10	40
		Mean value per female		
Number of implantation sites	12.05	13.14	13.00	12.48
Duration of gestation [days]	22.06	21.95	22.05	22.05
Number of living pups	11.05	12.57	11.76	11.91
Pups stillborn [% per group]	1.9	1.5	0.8	1.8
Pups found dead [N]	0	0	2 (1)	0
Weight of pups [g]	6.05	5.93	6.07	6.07
Sex ratio [%] male pups : total pups	50.83	51.19	53.99	47.25

() number of litters affected

The number of implantations, duration of gestation, # of living and dead F2 fetuses (litter size), and sex-ratio of F2 fetuses of the treated groups were not affected by BAY 59-7939 treatment. There were no changes in clinical findings of F2 pups. The body weight/growth of F2 fetuses was similar in control and treated groups. Other intrauterine development parameters are given in table above.

In conclusion, BAY 59-7939 Coprecipitate 10 % 100 treatment in pregnant dams produced maternal preterm delivery and, increased incidences of still birth, empty stomach and intestines in pups of 10 and 40 mg/kg/day groups treated dams. The developmental adverse effects of hypoactivity, pale skin, cold to touch surface, deficient sucking developmental reflex (no detectable milk spots in pups) were reported in F1 pups of dams of 10 and 40 mg/kg/day groups. The identified NOEL for the physical development and reflex and behavioral testing of the F1 generation after weaning was 2.5 mg/kg/day. The NOAEL for maternal effects (FO) and, pre- and postnatal development of the F1 generation was also 2.5 mg/kg/day and based on body surface area it was 2 times greater exposure than the proposed human dose.

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/s/

Marcus Cato

3/10/2009 07:12:35 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on March 9, 2009. The purpose of the meeting was to discuss the integrated analyses of symptomatic Venous thromboembolism (VTE) and death in RECORD 1-4.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: March 9, 2009
TIME: 3:30 PM - 4:00 PM EST
LOCATION: CDER WO 2327 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Statistical,

MEETING CHAIR: Dr. Jyoti Zalkikar

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Marcus Cato, M.B.A., Regulatory Health Project Manager

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS VII

Chava Zibman, Ph.D., Statistical Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

JOHNSON & JOHNSON

Leonard Oppenheimer, PhD. Statistical Sciences
John Zhang PhD. Statistical Sciences
Juliana Ianus, Ph.D. Statistical Sciences
Yingshan You, Data Programming

BAYER

Torsten Westermeier PhD Therapeutic Area Expert Statistician
Alice Benson PhD, Principal Statistician, Global Clinical Statistics,
Martin Homering PhD, Statistical Sciences
Patricia Hagerty Statistical Analyst - Global Statistical Programming

BACKGROUND:

In a teleconference on March 6, 2009, FDA inquired how J&J accounted for the different treatment durations in their pooled analysis of RECORD studies. The sponsor and FDA statisticians agreed to meet the week starting March 9, 2009, to discuss the pooled analysis in greater detail. On March 9, 2009, J&J submitted background information (see attached).

MEETING OBJECTIVES:

To discuss the integrated analyses of symptomatic VTE and death in RECORD 1-4.

DISCUSSION POINTS:

FDA stated it had reviewed the background information submitted by J&J. FDA stated it was preparing an information request regarding the integrated analysis and would send it soon. FDA has not been able to reproduce the data sets and would like to perform some analyses. J&J offered to perform analyses at FDA request. FDA stated it would like to perform them internally and get back to J&J. FDA requested a quick turn around on the information request.

DECISIONS (AGREEMENTS) REACHED:

- FDA would send an information request regarding the integrated analysis
- J&J would provide a quick turnaround on the information request

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- N/A

ACTION ITEMS:

- FDA to send an information request regarding the integrated analysis

ATTACHMENTS/HANDOUTS:

- J&J submitted background information

NDA 22-406 XARELTO™ (rivaroxaban)
Telecon March 9th to discuss Statistical Review

Summary of Rationale and Background of Integrated Analyses of Symptomatic VTE and death in RECORD 1-4

Integrated analyses of the RECORD studies are important for the standard reasons:

- to obtain more precise estimates of treatment differences
- to be able to explore important subgroups
- to be able to assess the effects of lower frequency outcomes

Prior to unblinding any of the RECORD studies both symptomatic VTE/death and bleeding was pre-specified as important endpoints to consider in a pooled analysis because of their clinical relevance in studying an anti-coagulant. Also it was realized that because of their low frequency we might not be able to fully elucidate treatment differences based on individual studies.

Although there were some differences among the four RECORD studies, there were many more similarities including the following:

- similar study designs and randomization processes
- similar rivaroxaban dose of 10 mg QD and start time
- similar CRFs/information collected in a similar manner
- similar inclusion/exclusion criteria
- similar visit schedules
- similar efficacy/safety definitions
- same central labs
- similar ascertainment procedures
- same central and blinded adjudication committees

A SAP for the integrated analysis of RECORD 1, 2 and 3 was prepared and finalized before the unblinding of any of the 4 RECORD studies. The composite of symptomatic

VTE (DVT, PE) or death from all causes was pre-specified as the primary efficacy endpoint for the integrated analysis from RECORD 1, 2 and 3. An updated analysis plan that described the analysis of the pooled RECORD 1-4 studies was finalized before the unblinding of RECORD 4 (Section 16.1, PH-35415 including the original plan).

The primary endpoint for the integrated analysis that included pooled data from the 4 RECORD studies or the separately pooled THR and TKR studies was the composite of symptomatic VTE (DVT, PE) or death from all causes during the double-blind treatment period in subjects valid for safety analysis. This endpoint was the primary objective of the pooled analysis since these events are clinically important and also because the assessment of these events was possible in all subjects regardless of the availability of an adequate venographic assessment. Other supportive endpoints examined included symptomatic VTE, PE, death, and the composite of PE or death. It should be noted that the composite of PE or death was not prespecified in the integrated SAP.

Since symptomatic VTE events could occur at any time during the study, the time to first event analysis was performed for detecting the treatment effect. Studies with different durations could be pooled for time to event analyses when subjects without events were censored at the end of either the treatment phase or the study. A Cox regression model was performed with study and treatment group as covariates to determine the hazard ratio and its 95% CI (rivaroxaban versus enoxaparin). The relative risk reduction was calculated as 100% x (1-hazard ratio). To assess study heterogeneity, an interaction test was performed for testing differential treatment effects across the 4 RECORD studies based on an asymptotic 2-sided p value from a Cox regression model with terms for treatment group, study, and a study by treatment interaction. The assumption for proportionality of the Cox model was also assessed. A Kaplan-Meier analysis was also done for accrued events over time for each treatment group. Similar analyses were conducted for individual studies and for components of the primary endpoint. The original RECORD 1-3 analysis for the European Union regulatory filing was to be based on absolute differences but this was changed to an odds ratio approach due to heterogeneity on the risk difference scale. The details of the planned analyses can be found in the Statistical Analysis Plan (Section 16.1, PH-35415).

The primary analysis for the pooled RECORD studies (1, 2, 3 and 4) was based on the "total duration pool", which was defined as the double-blind standard-of-care study medication phase (active and placebo control treatment) from all 4 RECORD studies. The "treatment phase" was defined as the time from the day of surgery (Day 1) until Day 42 (Day 36+6) for RECORD 1 and 2 and until Day 17 (Day 13+4) for RECORD 3 and 4. Supportive analyses were also performed for the following:

- "Pool until Day 12±2", which included events occurring during the double-blind treatment period until Day 12±2 for the pooled RECORD 1-4
- "Active control pool", which included events occurring during the active treatment periods for each study, excluding the placebo treatment period following enoxaparin treatment in RECORD 2 for the pooled RECORD 1-4
- Entire study period (treatment phase plus follow-up phase) for the pooled RECORD 1-4. The "follow-up phase" was pre-specified in the protocols as 30-35 days after the end of double-blind treatment, i.e. the time period after Day 42 in

RECORD 1 and 2, and after Day 17 in RECORD 3 and 4. All events occurring after Day 42/17 were considered in the Cox model

- Pooled RECORD 1-2 (THR) studies and pooled RECORD 3-4 (TKR) studies separately based on the same duration of the study period.

These results of the symptomatic VTE/death endpoint for the various pools for the pooled RECORD 1-4, which are summarized in the below table, were similar across the 4 analysis pools. The results of the pooled RECORD 1-2 (THR) studies were also similar to the pooled RECORD 3-4 (TKR) studies; these results are included in tabular and graphical format in Section 3.4.11.1 of the ISE.

Composite of Symptomatic VTE or Death
(Subjects Valid for Safety Analysis in the Pooled RECORD 1-4 Studies)

Analysis Pool	Rivaroxaban n (%) N=6183	Enoxaparin n (%) N=6200	ARD (95% CI)	HR (95% CI)
Total Duration – treatment phase	35 (0.57)	82 (1.32)	-0.76% (-1.10, -0.42)	0.42 (0.29, 0.63)
Total Duration – treatment plus follow-up phase	38 (0.61)	79 (1.27)	Not reported	0.48 (0.32, 0.70)
Treatment Phase until Day 12 +-2	29 (0.47)	60 (0.97)	-0.50% (-0.80, -0.20)	0.48 (0.31, 0.75)
Active Control Phase	32 (0.52)	67 (1.08)	-0.56% (-0.88, -0.25)	0.48 (0.31, 0.73)

Abbreviations: ARD=absolute risk difference; CI=confidence interval; DVT=deep vein thrombosis; HR=hazard ratio; PE=pulmonary embolism; VTE=venous thromboembolism

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/s/

Marcus Cato

4/1/2009 09:09:34 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on March 6, 2009. The purpose of the meeting was to discuss the upcoming advisory committee (AC) meeting.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: March 6, 2009
TIME: 3:00 PM - 4:00 PM EST
LOCATION: CDER WO 2376 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager
Min Lu, M.D., Clinical Reviewer
Diane Leaman, Safety Project Manager

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS VII

Chava Zibman, Ph.D., Statistical Reviewer

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer
Jyoti Zalkikar, Ph.D., Biostatistics Team Leader

EXTERNAL ATTENDEES:

JOHNSON & JOHNSON

Peter DiBattiste	M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters	M.D. Franchise Medical Leader
Lloyd Haskell	M.D. VP, CDTL
Paul Burton	M.D. Ph.D. F.A.C.C., Sr. Medical Director, Clinical Leader
Leonard Oppenheimer	Ph.D. Statistical Sciences
Deb Karvois	Project Scientist
Mehul Desai	M.D. Clinical
Jesse A. Berlin	ScD, VP, Epidemiology
G.K. (Dina) Anand	M.D., Post-Marketing Safety Franchise Leader
Yingshan You	Data Programming
Andrea Masciale	FDA Liaison Office, Regulatory Affairs
Steve Miller	VP, Global Regulatory Affairs
Michael Kronig	M.D., VP Cardiovascular Regulatory Affairs
Sanjay Jalota	MRPharmS, Regulatory Global Regulatory Lead
Donald L. Heald	Ph.D. VP and Global Head of Clinical PK
Achiel Van Peer	Ph.D. Global Sr. Scientific Leader Clinical Pharmacology
An Thyssen	Ph.D. Clinpharm Leader Rivaroxaban
Harry Flanagan	DO, Post-Marketing Safety Expert, Benefit Risk Management
Andrea Kollath	DVM, Regulatory Affairs
Sigmond Johnson	MS, MBA Program Coordinator
John Zhang	Ph.D. Statistical Sciences
Juliana Ianus	Ph.D. Statistical Sciences

BAYER

Frank Misselwitz	M.D. , Ph.d., VP Head Therapeutic Area CV & Coagulation
Joseph Scheeren	Pharm.D., SVP Head of Global Regulatory Affairs
Scott D. Berkowitz	M.D. FACP, FACC, VP, Head, Thrombosis & Hemostasis CV and Coagulation
Gerhard Schlueter	Regulatory Head of General Medicine/Cardiology
Alice Benson	Principal Statistician, Global Clinical Statistics
Martin Homering	Statistical Sciences
Patricia Hagerty	Statistical Analyst –Global Statistical Programming
Andrea Derix	Ph.D. Den. Global Regulatory Strategist
Larry Winick	MA Global Regulatory Strategist; Hematology/Cardiology
Dagmar Kubitza	Ph.D. Global Clinical Pharmacology Project Leader
Torsten Westermeier	Ph.D. Therapeutic Area Expert Statistician CC
Patricia Hagerty	Statistical Analyst- Global Statistical Programming
Aasia Bhatti	M.D. Deputy Director for Int'l Drug Safety Division
Bernard Glombitza	M.D. Global Project Leader Wuppertal, Germany

BACKGROUND:

N/A

MEETING OBJECTIVES:

To provide clarifications regarding FDA presentations and discuss expectations for the March 19, 2009, advisory committee meeting (AC).

DISCUSSION POINTS:

FDA provided an overview of their expectations for the AC. FDA is in the process of developing its presentations and will have a more solid understanding by the end of the week starting March 9, 2009. FDA has found it to be helpful that AC presentations are clear, simple and focused. FDA emphasized that all its comments are subject to change as the process is in flux and highly dynamic. In general FDA expects to present:

- An Introduction
  - FDA's perspective is that the AC will be part of an ongoing review,
  - An overview of oral anticoagulants
  - Ximelagatran 2004 AC committee review
  - Rivaroxaban introduction highlighting the uniqueness of the regulatory program.
- Regulatory background for prior drugs approved
- Overview of interim safety
- History of hepatotoxicity
- Discussion of the sponsor submitted risk management plan

FDA does not anticipate a focus upon efficacy in the FDA presentation. The FDA presentations will generally focus upon safety. FDA has not determined if clinical pharmacology slides will be presented to address the request for a lower drug dose. The safety questions to the AC are most likely to relate to bleeding and a possible signal for Liver toxicity. FDA also anticipates a question related to the overall risk benefit assessment.

J&J discussed its plans and mentioned their comments are subject to change as their process is fluid also. At the moment J&J has four speakers; two from the company and two consultants. J&J plans to present:

- An introduction,
- The current state of prophylaxis of DVT in orthopedic surgery in the context of the US and the rest of the world,
- The trail data with emphasis on efficacy,
- A safety presentation covering bleeding, cardiovascular concerns and a substantial liver presentation and possibly individual cases,
- A summary to include a safety surveillance plan and risk benefit assessment.

J&J inquired about its response to the February 5, 2009, Clinical Pharmacology discipline review letter. FDA stated it is still considering if it will present at the AC. FDA emphasized that if it does not present at the AC it is not because it does not regard the topic as important but rather the format of the AC may not lend itself to the complexity of the issue. FDA reiterated that increases in exposure in certain populations correspond to an increased risk of bleeding.

J&J asked if FDA viewed the lower dose development as a labeling issue or an approvability issue. FDA stated that it has not settled yet on an answer or if the feedback at the AC would be in the form of a discussion or a vote. J&J expressed that it would be very helpful to get AC input and recommended FDA present the information in a simple format that would allow for discussion.

J&J inquired about presentation topics. FDA reiterated the outline (see above).

FDA inquired how the sponsor accounted for the different treatment durations in their pooled analysis of RECORD studies. The sponsor and FDA statisticians agreed to meet the week starting March 9, 2009, to discuss in greater detail.

DECISIONS (AGREEMENTS) REACHED:

- N/A

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- AC presentations

ACTION ITEMS:

- FDA and J&J to meet the week starting March 9, 2009

ATTACHMENTS/HANDOUTS:

- N/A

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/s/

Marcus Cato

3/18/2009 12:13:32 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

INFORMATION REQUEST LETTER

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We are reviewing the Clinical Pharmacology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical Pharmacology

1) As discussed in our January 9, 2009, teleconference, an unexplained higher exposure to rivaroxaban in Japanese subjects compared to other tested groups was identified during our preliminary review of your application. It is possible that unmeasured or unreported environmental or demographic factors may have contributed to this difference in exposure to rivaroxaban. Furthermore, differences in genetic background in the disposition pathway of rivaroxaban may contribute. (b) (4)

(b) (4)

Gene	Caucasian	African	Chinese	Japanese
CYP3A4	7	20	5	6
CYP3A5	30	29	29	29
CYP2J2	109	106	109	107
ABCG2	105	101	101	101
ABCB1	287	310	281	274

[redacted] (b) (4)

(b) (4), and 3) Linkage Disequilibrium (LD) and haplotype structure differ for these genes across the four groups.

Since it is plausible that the PK differences seen in the Japanese population may be explained, at least in part, by genetic differences in any or all of the genes involved in rivaroxaban PK, we recommend that you analyze candidate (b) (4) haplotypes in order to rule out this cause of variability.

2) In two studies (Study 11864 and 11279), there appears to be a greater than additive response to clopidogrel-rivaroxaban co-treatment on the bleeding time endpoint. We note that clopidogrel PK samples were not obtained, but Pharmacogenomics (PGx) samples were banked.

   It is difficult to rule out a Pharmacokinetic Drug-Drug Interaction (PK DDI) because clopidogrel active metabolite concentrations were not measured. In the absence of these clopidogrel PK samples, we recommend that you consider genotyping patients for variants known to be determinants of clopidogrel response. These include, but are not limited to, CYP2C19 variants (e.g., *2, *3, *4, *5, *6, *8, *9, *10, *17). The *2 reduced function allele is expected to be most common in this Caucasian population. However, any divergence of allele frequencies from the expected frequency could implicate the clopidogrel metabolic pathway in a PK DDI. While the effect of rivaroxaban on various Drug Metabolizing Enzymes (DMEs) has been described, the clopidogrel metabolic pathway is complex and genotyping may offer PK-centric mechanistic hypotheses to the observed effect of co-treatment on bleeding time. This can also be tested by removing the issue of clopidogrel's metabolic complexity (it is a prodrug converted to an active metabolite) by studying a similar drug without the metabolic complexity (e.g., prasugrel).

3) We refer to our February 5, 2009, Clinical Pharmacology discipline review letter and our January 9, 2009, teleconference. We request a written response to our request for development of a lower strength tablet or scored 10 mg tablet by February 24, 2009.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, MD
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

2/19/2009 05:20:43 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

INFORMATION REQUEST LETTER

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We are reviewing the Clinical and Statistical sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical

1. Develop a table that summarizes the incidence (number of patients/percentage) of intracranial hemorrhage (using the broad definitions cited in study reports for various terms that refer to any form of bleeding within the skull--e.g., hemorrhage stroke, basal ganglia bleed, subdural hematoma, etc) among all RECORD studies as well as the Magellan and Atlas studies by active versus comparator groups.

2. Develop a table that summarizes the use (number of patients/percentage) of clopidogrel or ticlopidine during the post-treatment initiation period (active treatment period) in the RECORD studies by active vs. comparator groups.

3. Develop a table that summarizes the use of aspirin (number of patients/percentage) during the post-treatment initiation period (active treatment period) in the RECORD studies by active vs. comparator groups.

4. Develop a table that summarizes the use of non-steroidal anti-inflammatory drugs (NSAIDS, exclusive of aspirin) (number of patients/percentage) during the post-treatment initiation period (active treatment period) in the RECORD studies by active vs. comparator groups. NSAIDS are listed at the following web address: http://www.fda.gov/cder/drug/infopage/cox2/

5. In the response to the January 21, 2009 FDA requests, you summarize the occurrence of ALT> 3X ULN and TBL > 2X ULN (question 4) by race, for the RECORD studies. Please confirm that the shown table (where the total incidence is 0.15% for rivaroxaban and 0.11% for enoxaparin) includes both the active treatment and follow-up period. We are concerned this table might only include the data from the active treatment period.

Statistical

6. Re-submit bleeding event data (Pooled Study Record 1-4) including study drug variables and other important variables such as:

- Age,
- Gender,
- Venous thromboembolism (VTE) risk factor,
- History of VTE,
- Duration of surgery.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, MD
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

2/11/2009 05:38:47 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 10, 2009

TO: File

FROM: Diane Leaman

SUBJECT: **February 10, 2009 e-mail to Johnson and Johnson regarding Clinical information request.**

NDA 22-406, Xarelto (rivaroxaban) tablets

Andrea,

We would like to request the following information regarding the recently submitted rivaroxaban clinical laboratory datasets:

- Please clarify the data cut-off dates for ongoing studies for which lab datasets were submitted, and provide a brief statement of how the cut-off dates were decided and implemented.

- Please calculate mean duration of blinded study drug exposure at time of data cut-off for three ongoing studies for which laboratory datasets were submitted:
    - J-ROCKET-AF, (12620)
    - EINSTEIN DVT/PE, (11702)
    - ROCKET-AF, (11630)

- A quick evaluation of the data associated with Study 12620jrocket shows that this study includes a total of 1,185 subjects with a single treatment arm labeled BLINDED and coded 9999. Since there was more than one treatment arm in this study, please re-code the treatments using as an example the ROCKET study where the treatment arms are labeled DUMMY_A and DUMMY_B.

Diane Leaman
Safety Project Manager
Division of Medical Imaging and Hematology Products

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/s/

Diane V Leaman
2/10/2009 05:35:37 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on February 9, 2009. The purpose of the meeting was to discuss the February 5, 2009, Clinical Pharmacology discipline review letter.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: February 9, 2009
TIME: 3:00 PM - 4:00 PM EST
LOCATION: CDER WO 2376 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Young M Choi

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS

Richard Pazdur, M.D., Director

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Clinical Reviewer
Marcus Cato, M.B.A., Regulatory Health Project Manager
Diane Leaman, Safety Project Manager

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer
Brian Booth, Ph.D., Clinical Pharmacology Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/
PHARMACOMETRICS DIVISION

Christoffer Tornoe, Ph.D., Clinical Pharmacology Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL
PHARMACOLOGY/PHARMACOGENOMICS GROUP

Issam Zineh, Ph.D., Associate Director
Rosane Charlab Orbach, Ph.D., Clinical Pharmacology Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

J&J

Peter DiBattiste, M.D., F.A.C.C. VP Therapeutic Area Head CV
Gary Peters , MD Franchise Medical Leader
Leonard Oppenheimer, PhD. Statistical Sciences
Mehul Desai MD, Project Physician
Donald L. Heald, Ph.D. VP and Global Head of Clinical PK
Achiel Van Peer, Ph.D. Global Senior Scientific Leader Clinical Pharmacology
An Thyssen, PhD, Clinpharm Leader rivaroxaban
Harry Flanagan, MD Post-Marketing Safety Expert, Benefit Risk Management
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Kollath, DVM, Regulatory Affairs,
Sigmond Johnson, MS, MBA Program Coordination

BAYER

Andrea Derix, PhD, Sen. Global Regulatory Strategist
Alice Benson Principal Statistician, Global Clinical Statistics,
Martin Homering Statistical Sciences
Scott D. Berkowitz, MD, FACP, FACC, VP, Head, Thrombosis, Hemostasis, CV and Coagulation
Larry Winick MA Global Regulatory Strategist; Hematology/Cardiology
Dagmar Kubitza, PhD Global Clinical Pharmacology Project Leader, BSP
Torsten. Westermeier PhD, Statistical Sciences

BACKGROUND:

On February 5, 2009, FDA sent Johnson and Johnson Pharmaceutical Research and Development (J&J) a Clinical Pharmacology discipline review letter and a request to meet to discuss their pending response.

MEETING OBJECTIVES:

To discuss the February 5, 2009, Clinical Pharmacology discipline review letter.

DISCUSSION POINTS:

Discipline review letter point 1

FDA clarified its position regarding the February 5, 2009, Clinical Pharmacology discipline review letter. FDA emphasized that a clinically relevant increase in systematic exposure was noted in certain patient populations. FDA provided a clinical overview drawing attention to the relatively shallow dose response curve and steep dose bleeding curve for rivaroxaban compared to enoxapoarin as well as an almost five-fold risk of major bleeding in subjects receiving a daily dose of 10 mg vs 20 mg in the Phase 2 dose ranging study 11527. FDA identified several special populations (i.e., patients with renal impairment, hepatic impairment, and/or moderate/strong CYP3A4 or P-gp inhibitors) where clinically relevant increases in drug exposure could mimic the exposure difference seen from a doubling of the applicants proposed dose (i.e., 10 mg qd to 20 mg qd) were likely. FDA stated that without the ability for downward dose adjustment to match drug exposure between the general population and these special populations a part of the target population will not be able to utilize this drug. FDA again recommended that the

applicant develop a lower strength or scored 10 mg tablet. FDA also reminded the applicant that the 5 mg dosage form has been extensively studied as noted in the reports submitted in support of this application.

J&J highlighted specific bleeding rates from Phase 2 studies that dosed rivaroxaban bid rather than the proposed daily dosing regimen. FDA stated that a twice-daily dosing regimen is not a proposed drug dosage and that the focus for this product has been on study data using once-daily dosing because the exposure profiles are not the same. FDA reemphasized it does not agree with the J&J position that only a ≥ 2 fold change in exposure is clinically relevant and it believes that a clinically relevant change in exposure is likely lower given the safety data from the Phase 2 dose ranging study 11527. FDA stated that this is a potential labeling issue and if a lower strength were developed it would work with the applicant to match rivaroxaban exposure in the special populations with the general population rather than restrict its use.

FDA asked J&J to clarify its reluctance to downward titrate the dose. J&J expressed concern that matching exposure in subpopulations may not produce the same efficacy and cited efficacy data from the 5mg qd vs. 10 mg qd in the Phase 2 dose ranging study 11527. FDA explained that this comparison was not appropriate because the exposure differences that were being discussed were similar to going from a 10 mg qd regimen to a 20 mg qd regimen and the dose response curve compared to enoxaparin was shallow. J&J also inquired if efficacy studies would be necessary in patient subpopulations using a 5mg dosage form. FDA advised that development of the 5 mg strength could be justified based on the pharmacokinetic/pharmacodynamic (PK/PD) characteristics.

J&J inquired if this was viewed by FDA as an approvability issue. FDA stated that if this issue was not resolved prior to the advisory committee (AC) meeting there may be discussion at the AC and it could be an issue for approval.

Discipline review letter point 2

FDA is not persuaded by the J&J explanation regarding an approximately 40% higher exposure of rivaroxaban in Japanese subjects compared to other ethnic groups. FDA and J&J discussed details of the FDA data analysis. FDA emphasized that the key point was Figure 3 (see discipline review letter) where Chinese and Japanese subjects show the same PK/PD relationship but different exposure rates. In response, the sponsor inquired if they might submit age differences in a pooled analysis. FDA agreed. FDA also provided additional clarification to the sponsor regarding its request for additional exploration into potential pharmacogenomic causes.

DECISIONS (AGREEMENTS) REACHED:

- J&J to submit pooled analysis of age differences between Chinese and Japanese in studies 11126 and 11608

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- J&J development of a lower strength tablet (in addition to the proposed 10 mg tablet) or a scored 10 mg tablet

ACTION ITEMS:

- J&J to submit pooled analysis of age differences between Chinese and Japanese in studies 11126 and 11608
- J&J to submit its decision regarding development of a lower strength tablet (in addition to the proposed 10 mg tablet) or a scored 10 mg tablet.

ATTACHMENTS/HANDOUTS:

February 5, 2009, Clinical Pharmacology discipline review letter

5 pages have been withheld immediately following this page as this is a duplicate of the letter electronically dated 2.5.09 in this Administrative Section

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/s/

Marcus Cato

3/6/2009 06:24:50 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

DISCIPLINE REVIEW LETTER

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to your submission dated December 19, 2008.

Our review of the Clinical Pharmacology section of your submission is ongoing, and we have identified the following deficiencies. PK and PD refer to pharmacokinetic and pharmacodynamic, respectively:

1. We have reviewed your response and supporting data addressing the request to develop a lower strength tablet (in addition to the proposed 10 mg tablet) or a scored 10 mg tablet. Your response indicated that you did not envision a need for a lower strength tablet or a scored 10 mg tablet. You supplied information justifying your perspective. We are not persuaded by your justifications. As outlined in Table 1 and Figure 1 of your response, there is a steep dose response relationship, relative to enoxaparin, for the risk of major bleeding events. These major bleeding events are defined as a fatal bleeding event, bleeding into a critical organ (i.e., retroperitoneal, intracranial, intraocular, or intraspinal bleeding), bleeding that required re-operation, clinically overt extrasurgical site bleeding associated with a ≥2 g/dL decrease in hemoglobin concentration, or clinically overt extra-surgical site bleeding leading to transfusion of ≥2 units of whole blood or packed cells. Table 1 in your response to FDA reports a greater than 4 fold increase in major bleeding (0.7% vs. 4.3%) when exposure is increased two fold from the proposed dose. This suggests that even a 1.5 fold increase in exposure may double the risk of major bleeding. This is an important safety concern.

   Without the ability to downward titrate the proposed dose of rivaroxaban the following populations may be potentially at increased risk for major bleeding based on the exposure and PD data you submitted (i.e., clotting factor Xa (FXa) inhibition and prothrombin time (PT)): 1) moderate to severe renal impairment, 2) mild to severe renal impairment when used with a cytochtome P450 exzyme 3A4 (CYP3A4) inhibitor, 3) moderate to severe hepatic impairment, and 4) concurrent use with a moderate or strong CYP3A4 inhibitor plus a moderate or strong P-glycoprotein (Pgp) inhibitor. Further, the potential increase in exposure from renal impairment combined with a CYP3A4 inhibitor is of particular concern given it was not studied and could be significant given both major elimination pathways are blocked.

Therefore, without downward dose adjustment, a significant part of the target population will not be able to utilize rivaroxaban and inappropriate use of the current strength in these populations could pose an unacceptable risk (e.g., medication error). We again strongly recommend you to develop a lower strength tablet or a scored 10 mg tablet of rivaroxaban and provide adequate data to support bioequivalence between the current formulation and the lower strength or scored 10 mg tablet. We encourage you to promptly obtain this information and submit it as an amendment to your application. Alternative methods to address this safety issue (e.g., restricted distribution or other types of limitations of access) will be considered but we maintain that the issue is best addressed by the development of a lower strength tablet or a scored 10 mg tablet. We suggest having a teleconference to further address our safety concerns. This will afford us an opportunity to further clarify our position and discuss any additional questions or comments you may have on this matter.

2. We have reviewed your response and supporting data regarding an approximately 40% higher exposure of rivaroxaban in Japanese subjects compared to other ethnic groups including Chinese and we are not persuaded by your explanation. Based on preliminary analysis, we find that the median maximum plasma concentration (C_{max})/Dose and area under the curve (AUC)/Dose were approximately 50% higher in Japanese compared to other ethnicities (see Figure 1).

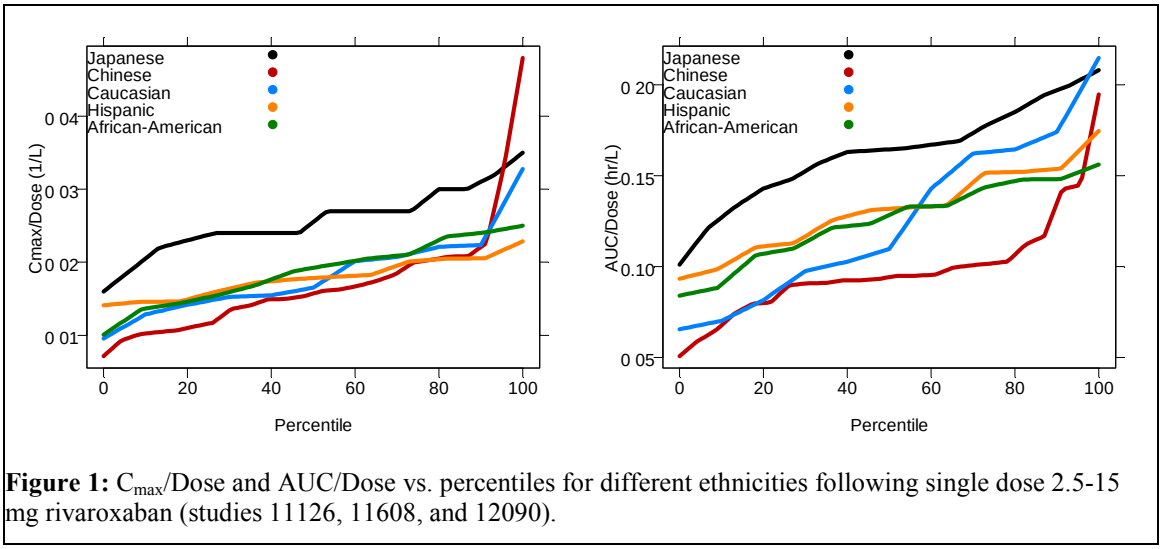

Figure 1: C_{max}/Dose and AUC/Dose vs. percentiles for different ethnicities following single dose 2.5-15 mg rivaroxaban (studies 11126, 11608, and 12090).

The only apparent differences in covariates for Japanese compared to other ethnicities are body weight and age where the Japanese were the youngest and "lightest" subjects (see Figure 2) potentially explaining the higher exposure.

However, the exposure in Japanese was approximately 50% higher compared to Chinese subjects weighing the same as Japanese. The Japanese were approximately 10 years younger than the Chinese (mean age of 23 and 34 years for Japanese and Chinese subjects in studies 11126 and 11608, respectively). One would therefore expect the younger Japanese subjects to clear the drug faster (age was found to be a covariate for clearance in population PK) and thus lower exposure (AUC). The opposite was observed in studies 11126 and 11608.

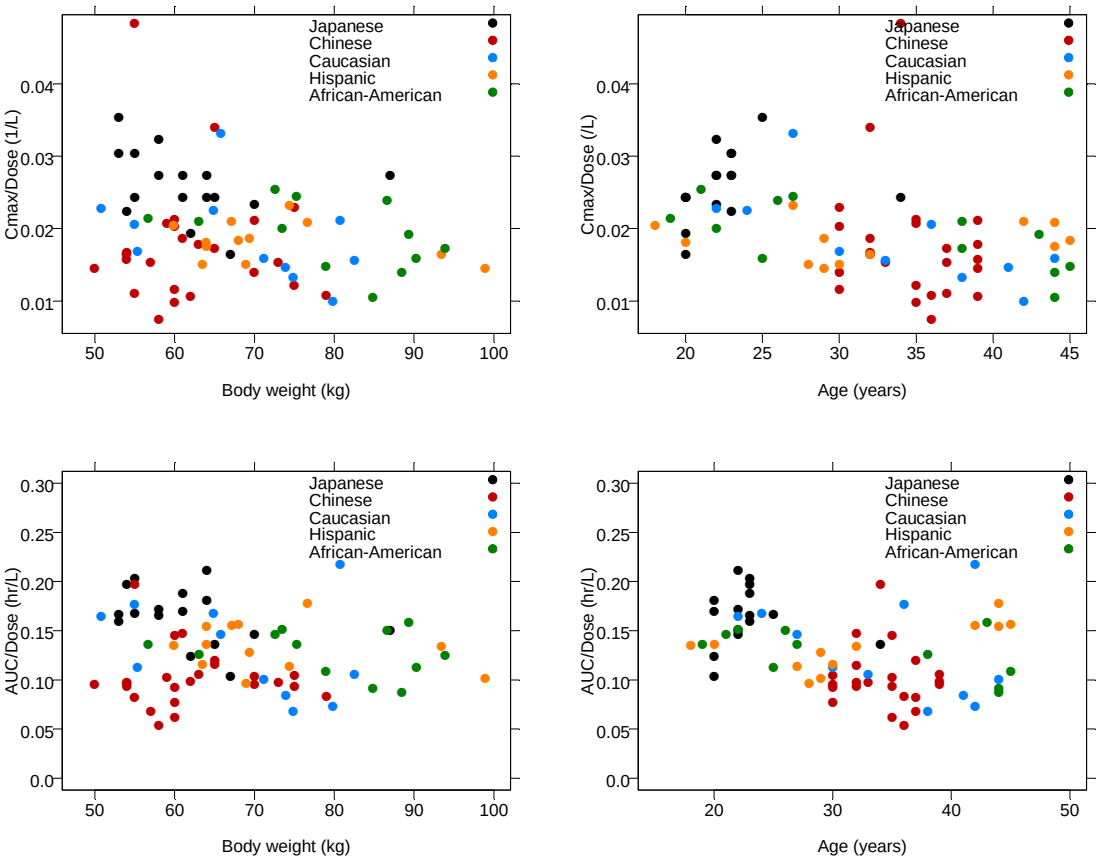

Figure 2: C_{max}/Dose (Top) and AUC/Dose (Bottom) vs. body weight (Left) and age (Right) following single dose 2.5-15 mg rivaroxaban from studies 11126, 11608, and 12090.

No apparent inter-ethnicity differences were found for Factor Xa inhibition between Japanese (study 11126) and Chinese (study 11608) subjects after adjusting for exposure differences following 10 mg single dose rivaroxaban (see Figure 3).

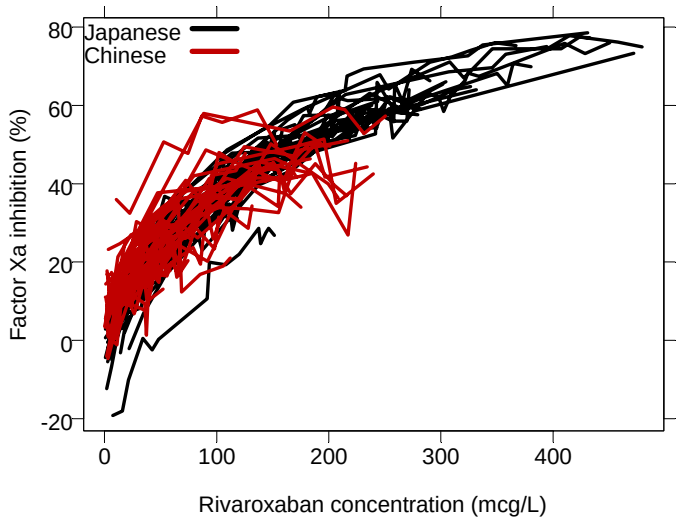

Figure 3: Factor Xa inhibition vs. rivaroxaban concentration in Japanese (black lines) and Chinese (red lines) subjects following 10 mg single dose rivaroxaban.

Based on the PK/PD data from studies 11126 and 11608 in Japanese and Chinese subjects, we conclude that there are significant differences in rivaroxaban pharmacokinetics for Japanese subjects compared to other ethnicities.

Given these preliminary findings and additional clarification we again ask you to provide an additional explanation for the higher exposure in the Japanese population. Pharmacogenetic differences should be considered in detail, in addition to other factors, in your response.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have questions, contact Marcus Cato, Regulatory Project Manager, at (301) 796-3903.

Sincerely,

{See appended electronic signature page}

Young M Choi, Ph.D.
Clinical Pharmacology Team Leader
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Young-Moon Choi

2/5/2009 05:20:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on February 2, 2009. The purpose of the meeting was to provide clarifications in regard to studies in your NDA and discuss expectations for the March 19, 2009, advisory committee meeting.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: February 2, 2009
TIME: 3:00 PM - 4:00 PM EST
LOCATION: CDER WO 1415 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Dwaine Rieves

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Rafel (Dwaine) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Marcus Cato, M.B.A., Regulatory Health Project Manager

OFFICE OF TRANLATIONAL SCIENCE/OFFICE OF BIOSTATISTICS

Ted Guo, Ph.D., Statistician,
Chava Zibman, Ph.D., Staff Fellow
Antonio Paredes, Ph.D., Statistician

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY/DIVISION OF EPIDEMIOLOGY I

Kate Gelperin, M.D., M.P.H., Medical Officer
Allen D Brinker, M.D., Medical Team Leader

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY 5

Young M Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer

OFFICE OF BIOSTATISTICS/DIVISION OF BIOMETRICS V

Qing Xu, Ph.D., Statistical Reviewer

OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

John R. Senior, M.D., Medical Officer (Hepatotoxicity)

EXTERNAL CONSTITUENT ATTENDEES:

J&J

Peter DiBattiste, MD, Therapeutic Area Head Cardiovascular
Gary Peters , MD Franchise Medical Leader
Leonard Oppenheimer, PhD. Statistical Sciences
Mehul Desai MD, Clinical
Jesse A. Berlin, ScD, VP, Epidemiology
G.K. (Dina) Anand MD, Post-Marketing Safety Franchise Leader
Yingshan You, Data Programming
Andrea Masciale, Regulatory Affairs, FDA Liaison Office
Steve Miller, VP Global Regulatory Affairs
Michael Kronig, MD, VP Cardiovascular Regulatory Affairs
Sanjay Jalota, MRPharmS, Regulatory Global Regulatory lead
Andrea Kollath, DVM, Regulatory Affairs

BAYER

Frank Misselwitz, MD, PhD, VP, Head Therapeutic Area CV and Coagulation
Joseph Scheeren, Pharm.D., SVP Head of Global Regulatory Affairs
Scott D. Berkowitz, MD, FACP, FACC, VP, Head, Thrombosis, Hemostasis, CV and Coagulation
Gerhard Schlueter,-Global Regulatory Affairs, Head of Therapeutic Area General Medicine
Andrea Derix, PhD, Global Regulatory Affairs,
Alice Benson Principal Statistician, Global Clinical Statistics,
Martin Homering Statistical Sciences
Patricia Hagerty Statistical Analyst - Global Statistical Programming

BACKGROUND:

On January 23, 2009, FDA requested a meeting with Johnson and Johnson Pharmaceutical Research and Development (J&J).

MEETING OBJECTIVES:

To provide clarifications in regard to studies in the NDA and discuss expectations for the March 19, 2009, advisory committee meeting (AC).

DISCUSSION POINTS:

In response to questions about patients who were to receive pneumatic compression J&J provided a written response (see attached). FDA stated that it appears patients who planned to undergo pneumatic compression were excluded from RECORD studies. FDA asked if this was captured in the case report forms. J&J stated that it was and they could submit a summary table to FDA.

FDA stated that in regard to the international aspect of their RECORD studies J&J should be prepared provide comment at the AC about perioperative management and how surgical procedures may vary internationally. FDA noted that approximately 85% of J&J's studied RECORD patients came from outside the United States (US). FDA asked if J&J could comment on how the studies are applicable to the US in their presentation.

J&J noted that they had incorporated tables in the NDA by country and that most of the US data is derived from the Record 4 study and that results had been similar. J&J expected some diffrenences in demographic data and perioperative management but they don't expect significant differences.

FDA & J&J discussed bleeding severity and concomitant medications use. FDA expressed concern for plavix/ticlide use in the US. J&J stated they have some data that they could submit but had not done specific analysis on major bleeding. J&J stated they would gather this data and prepare a submission. FDA stated it would prepare and send specific questions to J&J.

FDA provided its perspective for the AC:

FDA has not completed its review. The AC will be considered part of the review and FDA plans to focus on the major items identified to include:

- A summary of data from major studies
- Major efficacy
- Major safety (i.e., bleeding risks, liver toxicity, etc.)
- Logistical concerns (i.e., presentation, packaging, concomitant medications use, etc.)
- Ongoing clinical studies

FDA noted that its focus will generally be more on safety than efficacy although the totality of originally submitted data will be reviewed. FDA does not anticipate discussing a risk evaluation and mitigation strategy (REMS) in any detail. In general, FDA anticipates that a portion of the questions for AC will focus on the risk vs. benefit of the drug.

FDA & J&J discussed possible packaging and drug presentations that might be less conducive to "off-label" use. FDA advised that the discussion is appropriate to have after the AC, however FDA is concerned and J&J should be prepared to comment.

J&J inquired about FDA liver toxicity concerns. FDA stated that it will attempt to inform J&J of specific cases that might be presented at the AC but that is not certain as of now. FDA stated for the liver cases, there does not generally appear to be a definitive causative relationship based on our preliminary review but the data are still under review; the lack of long term data was of concern with respect to potential liver toxicity. In regard to pre-clinical questions FDA advised J&J to be prepared to address all FDA concerns, and FDA would work to share any specific concerns. J&J stated that it would take a broad approach in its briefing book for the AC.

J&J asked about the need for an orthopaedic surgeon they had consulted to be available at the AC for questions. FDA stated it may be useful for him/her to be there and it may be helpful for him/her to provide comment/a presentation on the international nature/surgical practice correlates for evaluating the RECORD data.

DECISIONS (AGREEMENTS) REACHED:

- J&J stated that they would submit a summary table of pneumatic compression patients excluded from RECORD studies to FDA/as well as a summary of pneumatic compression usage in RECORD studies (consistent with available data).
- FDA stated it would prepare and send specific questions to J&J in regard to bleeding severity and concomitant medications use.

- FDA stated that it will attempt to inform J&J of specific liver cases that might be presented at the AC.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- None.

ACTION ITEMS:

- J&J to submit a summary table of pneumatic compression patients excluded from RECORD studies to FDA and pneumatic usage in RECORD studies.
- FDA to prepare and send specific questions to J&J in regard to bleeding severity and concomitant medications use

ATTACHMENTS/HANDOUTS:

J&J written response Intermittent Pneumatic Compression (IPC)

NDA 22-406 Xarelto™ (rivaroxaban) January 28, 2009

Intermittent Pneumatic Compression (IPC)

While mechanical methods of thromboprophylaxis such as Intermittent Pneumatic Compression (IPC) have been shown to reduce the risk of DVT in a number of patient groups, they have been studied much less intensively than anticoagulant-based approaches and they are generally less efficacious than anticoagulant thromboprophylaxis. The primary reason why the use of IPC devices during the active treatment period was an exclusion criterion in the RECORD studies is that this modality is recommended by the American College of Chest Physicians primarily for use in patients at high risk of bleeding (Grade 1A recommendation). These patients are therefore not eligible for anticoagulant prophylaxis. In addition, although adjunctive use of IPC with anticoagulant therapy is possible, since IPC use would not be randomized it could represent a confounding factor for the primary efficacy analyses. Moreover, the amount of data supporting this combined use is limited. It should also be noted that the benefit of IPC devices was determined years ago when hospital stays were much longer than they are today (now usually only 2-4 days in the United States), and that it is difficult to implement their use effectively (e.g. studies have shown that the devices are often removed for prolonged periods of time even while in the hospital room).

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/s/

Marcus Cato

2/13/2009 12:09:21 PM

MEMORANDUM OF TELEPHONE CONVERSATION

NDA: 22-406

Date: January 30, 2009

FDA Participants:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Marcus Cato, M.B.A., Regulatory Health Project Manager

EXTERNAL Participants:

JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Andrea F. Kollath, DVM, Regulatory Affairs

Discussion:

Ms. Kollath called to gather information about the upcoming teleconference (February 2, 2009) between FDA and Johnson and Johnson (J&J). Ms. Kollath wanted to know who was invited to the teleconference from FDA and who should be included from J&J. I told her that clinical/chemistry/pre-clinical/clinical pharmacology/statistics and persons from the office of surveillance and epidemiology were invited, however the discussion would center around clarifications regarding liver datasets, clarifications in regard to the international aspect of their RECORD studies/international surgical practices and clarification in regard to why patients who were to receive pneumatic compression were excluded from their RECORD studies.

Ms. Kollath asked would it be appropriate for J&J to ask questions about the upcoming Advisory Committee meeting specifically what to include/focus on in their briefing document. I told her that it would be acceptable to ask that question at the meeting.

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/s/

Marcus Cato
2/3/2009 05:23:38 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on January 23, 2009. The purpose of the meeting was to discuss our January 21, 2009, clinical information request.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: January 23, 2009
TIME: 9:20 AM - 10:15 AM EST
LOCATION: CDER WO 2189 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Min Lu

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Min Lu, M.D., Clinical Reviewer
Marcus Cato, M.B.A., Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Andrea F. Kollath, DVM, Regulatory Affairs
Mehul Desai, MD, Project Physician, Clinical

BACKGROUND:

On January 21, 2009, FDA sent Johnson and Johnson Pharmaceutical Research and Development (J&J) a clinical information request via e-mail.

MEETING OBJECTIVES:

To Clarify the FDA clinical information request and the timeline for the J&J response.

DISCUSSION POINTS:

FDA & J&J discussed the details of the January 21, 2009, request. FDA provided clarifications. J&J stated that the majority of the information requested was ready and would be submitted on January 23, 2009. J&J further stated that any information that could not be submitted on January 23, 2009, would be submitted on January 26, 2009. FDA agreed.

DECISIONS (AGREEMENTS) REACHED:

- Information that could not be submitted by J&J on January 23, 2009 would be submitted on January 26, 2009.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- None.

ACTION ITEMS:

- J&J to submit information requested on January 21, 2009.

ATTACHMENTS/HANDOUTS:

January 21, 2009 FDA clinical information request one

1. For subject 11354-300014007, provide all local and central LFT results including Day 65 and after (not in narrative).

2. For subject 11355-60009-5028, provide LFT data after Day 55 and any additional follow-up information regarding clinical adverse events.

3. For subject 11357-55003-7007, provide hospital summary, all relevant hepatitis and other serology test results.

4. Provide summary tables as Table 1-2 [Pooled Incidence Rates of Liver-related Postbaseline Laboratory Abnormalities – After Day 0 Baseline (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)] under ISLS by race (White, Asian, and others as separate tables).

5. For subject 10944-84008, provide hospital summary, liver histological assessment by (b) (4) LFT result link and figure of LFT values over time (similar to LFT figures for other subjects).

6. For adjudicated cardiovascular events that occurred off-treatment, list the days relative to the last dose of active treatment for each event for both treatment group.

7. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 1-11 [Incidence of Postbaseline Hepatic Disorder Adverse Events (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)] for subjects under the following categories:
    - MSSO: Cholestasis and jaundice of hepatic origin
    - MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
    - MSSO: Hepatitis, non-infectious
    - MSSO: liver infections
    - MSSO: Possible liver-related coagulation and bleeding disturbances

8. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 2-7 [Incidence of Treatment-Emergent Adverse Events in the MSSO Search Category 'Hepatic Disorders' in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects

Valid for Safety in Studies 10942, 10944, 10945, and 11527)] for subjects under the following categories:

- MSSO: Cholestasis and jaundice of hepatic origin
- MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
- MSSO: Possible liver-related coagulation and bleeding disturbances

9. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 2-14 [Incidence of Treatment-emergent Adverse Events for "Hepatic Disorders" in Phase 2 Treatment Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 11223 and 11528)] for subjects under the following categories:
    - MSSO: Cholestasis and jaundice of hepatic origin
    - MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
    - MSSO: Liver infections
    - MSSO: Liver neoplasms, benign

January 21, 2009 FDA clinical information request two

1. For subject 16018-1005 in ongoing study, provide hospital summaries and full autopsy report.

2. Provide summary of Liver Advisory Panel assessment for other cases with increased ALT in RECORD studies (exclude those with ALT >3 x ULN concurrent with TB>2xULN).

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/s/

Marcus Cato

1/28/2009 04:44:53 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on January 16, 2009. The purpose of the meeting was to discuss our January 12, 2009, clinical information request.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3603.

Sincerely,

{See appended electronic signature page}

Marcus Cato, M.B.A.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: January 16, 2009
TIME: 2:30 PM - 3:00 PM EST
LOCATION: CDER WO 2189 conf Rm, Bldg22
APPLICATION: NDA 22-406
SPONSOR: Johnson and Johnson Pharmaceutical Research and Development
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Clinical, Guidance

MEETING CHAIR: Dr. Kathy Robie Suh

MEETING RECORDER: Mr. Marcus Cato

FDA ATTENDEES:

OFFICE OF NEW DRUGS/ OFFICE OF ONCOLOGY DRUG PRODUCTS/
DIVISION OF MEDICAL IMAGING AND HEMATOLOGY PRODUCTS

Kathy Robie Suh, M.D., Ph.D., Clinical Team Leader, Hematology
Min Lu, M.D., Clinical Reviewer
Diane Leaman, Safety Regulatory Health Project Manager
Marcus Cato, M.B.A., Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

JOHNSON & JOHNSON PHARMACEUTICAL RESEARCH AND DEVELOPMENT

Andrea Kollath, Regulatory Affairs
Sanjay Jalota, Regulatory Global Regulatory lead

BACKGROUND:

On January 12, 2009 FDA send Johnson and Johnson Pharmaceutical Research and Development (J&J) a clinical information request via e-mail.

MEETING OBJECTIVES:

To Clarify FDA clinical information request

DISCUSSION POINTS:

Request one

In regard to the FDA Request one (see attached clinical information request), FDA stated the subject was incorrectly identified, and the full autopsy report was available. J&J had noted the error and stated a link to the liver function test and any hospital summary would be available the week of January 19, 2009.

Request two and three

J&J stated that FDA Requests two and three (see attached clinical information request) will be available the week of January 19, 2009.

J&J asked if FDA could meet prior to the advisory committee meeting to discus noted liver cases, liver data, and a proposed Risk Evaluation and Mitigation Strategy (REMS). FDA stated it did not appear likely, but FDA would discuss the request internally and inform J&J if a discussion is deemed necessary.

J&J updated FDA with plans for its upcoming submissions. J&J stated a six-month (6-month is ok here) safety update would be submitted the week of February 16, 2009.

DECISIONS (AGREEMENTS) REACHED:

- None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

- REMS Discussion between FDA & J&J prior to the advisory committee meeting.

ACTION ITEMS:

- FDA to discuss meeting internally and inform J&J if a discussion is deemed necessary.
- J&J to make various submissions including a 6-month safety update

ATTACHMENTS/HANDOUTS:

January 12, 2009 FDA clinical information request

1. For subject 11355-140165153 who died of fatal bleeding, provide a full autopsy report, hospital summary, lab data including LFTs and coagulation tests during the treatment and in hospital before death, and investigator assessment for the event.

2. Clarify the number of cardiovascular events in RECORD trials. The discrepancy is noted in the number of events between the individual RECORD study reports and ISS report (Table 1-22).

3. Provide summary of number of patients with maximum ALT>3 ULN and maximum TB>2 ULN (not concurrent) for all completed studies and provide link to narrative and CRF. Also provide this information for ongoing studies if available.

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/s/

Marcus Cato

1/28/2009 04:42:12 PM

RECORD OF TELEPHONE CONVERSATION

NDA: 22-406

Today's date: January 27, 2009

Speakers: Dwaine Rieves for FDA
Michael Kronig for Johnson and Johnson/VP Reg Affairs

I returned a phone call to Dr. Kronig because he had left a voice mail for me yesterday. Dr. Kronig expressed some concern about timeliness of getting feedback from FDA since the company's briefing document is due relatively soon. I noted that we're doing the best we can and have a telephone conference schedule for next week. I noted that in general, the conference will focus upon:

1) clarification of the status of use of pneumatic compression in the RECORD studies/specifically were subjects excluded from all 4 studies if pneumatic compression was planned?/if so, did the case report forms actually capture any use of pneumatic compression/if so what was the usage between treatment groups? I noted that that AAOS regards pneumatic compression as useful in DVT prevention in knee/hip surgery and regards it, in many cases, as preferable to any drug therapy prophylaxis.

2) explanation of why the predominance of patients were enrolled outside of the USA/particularly since surgical and perioperative management may importantly differ in certain countries and hip/knee surgery apparently is very common in the USA. I encouraged them to address the question of the extent to which regional differences in perioperative care impact DVT rates/occurrence.

3) we hope to discuss the "liver data" situation and provide clarification re: our advisory committee focus. I noted that, in general, we will probably focus upon the details within the original NDA plus the summary tabulation/safety updates provided for on-going studies.

I briefly highlighted a few other concerns, as follows:

a) We need a summary of all intracranial hemorrhage across all studies. I expressed particular concern about the reports of intracranial hemorrhage in the ATLAS study that, in multiple cases, appeared related to the concomitant use of Plavix with rivaroxaban and I noted that the company must provide clarity regarding the use of any concomitant anti-platelet (as well as other coagulation-related drugs) throughout the proposed time course of rivaroxaban use. In particular, I expressed concern that, in practice, surgeons may readily direct resumption of concomitant medications within a few days following completion of surgery and, for many patients, these concomitant medication may include Plavix (or other coagulation-related products). I noted the proposed plans do not appear to address this issue.

b) I expressed concern that the logistical packaging programs for rivaroxaban does not appear well thought-out. I noted that, as currently proposed, the packaging appears very conducive to "off label" usage. I noted that the company needs to focus upon package that is more practical and conducive to the "short term" usage proposed in the application. For example, they may wish to consider use of "blister packs" of finite amount of drug or other unique packaging consideration. I noted that I anticipated this topic is likely to come up at the advisory committee and I suggested the company focus upon a well thought out/reasonable answer or justification.

c) I noted that our advisory committee documents and presentation may include discussion of other drugs that had liver-related problems, such as ximelagatran and/or one of the anti-diabetic drugs and potentially other drugs.

d) I noted these are only highlights and we hope to have a useful discussion within the next several days.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Rafel Rieves
1/28/2009 11:28:17 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 25, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to the teleconference between representatives of your firm and the FDA on January 9, 2009. The purpose of the meeting was to discuss the navigation of the Case Report Form (CRF) information in the December 18, 2008 submission to NDA 22-406.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Safety Project Manager
Division of Medical Imaging and
Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

MEETING DATE: January 9, 2009
TIME: 2:30 PM to 3:00 PM
LOCATION: White Oak Campus, Bldg 22, Room 2189
APPLICATION: NDA 22-406
DRUG NAME: Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING: Type A, Clinical

MEETING CHAIR: Dr. Min Lu

MEETING RECORDER: Ms. Diane Leaman, Safety Project Manager

FDA ATTENDEES:

Office of Oncology Products/Division of Medical Imaging and Hematology Products (DMIHP)

Min Lu, M.D., Medical Officer
Diane Leaman, Safety Regulatory Health Project Manager
Marcus Cato, Regulatory Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Johnson & Johnson

Andrea Kollath DVM, Director Regulatory Affairs
Sanjay Jalota MRPharms, Senior Director, Regulatory Affairs
Mehul Desai MD Director, Clinical Scientist
Shelly Chandler, Regulatory Operations

BACKGROUND:

On December 18, 2008 (received December 19, 2008), J&J submitted a response to an information request from DMIHP for electronic laboratory data and Case Report Forms (CRFs) relevant to drug-induced liver injury in all completed and ongoing clinical trials with Rivaroxaban.

MEETING OBJECTIVES:

To assist the Medical Officer in navigating the electronic information submitted in the December 19, 2008 submission.

DISCUSSION POINTS:

J&J clarified that central laboratory data were not included in the CRFs; only local laboratory data are in the CRFs. Central laboratory data are in a separate table.

All Phase 3 studies had central and local laboratory data. The sponsor is not sure whether all Phase 2 studies had data from both laboratories. The Medical Officer asked where the liver data was in the CRFs. The sponsor responded that they would research that and get back to the division with a response later.

J&J guided the Medical Officer to several areas in the submission where patient data was to be found. The sponsor noted that there were results from only six autopsies available. The medical officer noted that the submitted autopsy reports did not include two deaths (10844-84008 and 11223-506006) with the autopsies performed. The sponsor indicated that the available autopsy information for the patient who died in the Phase 2 trial is included in the NDA. There is a full, five-page report for patient 10944-84008 in a pdf file. There is a six-page copy of the original autopsy report for patient 11223-506006.

DECISIONS (AGREEMENTS) REACHED:

The sponsor will determine the location of the liver data in the CRFs and update DMIHP with the information.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

The location of the liver data, including chemistry data, in the CRFs needs to be determined.

ACTION ITEMS:

J&J will inform DMIHP of the location of the liver data in the CRFs.

ATTACHMENTS/HANDOUTS:

None.

POSTMEETING ADDENDUM:

On January 9, 2009, at 3:40 PM, J&J provided the following information via electronic mail:

Autopsy report for Subject 10944-84008.
This report is in Appendix 2 of the Integrated Summary of Liver Safety in the initial NDA (Sequence 0000)
Autopsy report for Subject 11223-506006.
This English translation is in the narrative in the MRR for Study 11223 (MRR-00150 ODIXa-DVT: Phase II dose finding and proof of principle trial in patients with acute symptomatic proximal deep vein thrombosis)(pages 1-1211 to 1-1217) in Module 5.3.5.4 of the initial NDA (Sequence 0000). The original report in local language has been requested and will be sent to FDA as soon as received.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Diane V Leaman
1/23/2009 04:05:16 PM

MEMORANDUM OF E-MAIL INFORMATION REQUESTS/CORRESPONDENCE

DATE:	January 12, 2009 – April 6, 2009
APPLICATION NUMBER:	NDA 22-406

BETWEEN:

Name:	Andrea F. Kollath, DVM, Director, Regulatory Affairs
e-mail:	AKollath@its.jnj.com
Representing:	Johnson and Johnson Pharmaceutical Research and Development

AND

Name:	Marcus Cato, M.B.A., Regulatory Project Manager Division of Medical Imaging and Hematology Products HFD-160

SUBJECT:	NDA 22-406 information requests/correspondence

Cato, Marcus

From: Cato, Marcus
Sent: Monday, April 06, 2009 1:34 PM
To: Kollath, Andrea [PRDUS]
Cc: 'Jalota, Sanjay [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following clinical pharmacology information within 10 business days.

Submit a revised file COLLEC.XPT (M5/P3 dataset folder in the 000 submission) in SAS transfer format that includes additional columns identifying patients (based on tables 14.3.5/ 9.1.1 through 14.3.5/ 9.7.2 in the report 35415) who received: 1) any platelet aggregation inhibitor, 2) aspirin or products containing aspirin, 3) clopidogrel, 4) any Non-steroidal anti-inflammatory drugs (NSAID) or combination product containing an NSAID, 5) Any CYP 3A4 inhibitor, and 6) Any P-gp inhibitor. This information should be formatted in a manner similar to CYP3A4 inducers that is already included in this data set. For Items #5 & #6 please also include a column identifying the name(s) of the CYP3A4 inhibitor(s) and a column identifying the name(s) of the P-gp inhibitor(s). In addition please include a revised define.pdf file for this dataset.

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
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(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, April 01, 2009 2:20 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22-406 information request

Importance: High

Dear Andrea,

We request that you submit the following information on or before April 2, 2009.

1. Provide a phone number, email address, and FAX number for the following three RECORD 4 investigators: Dr. John Ward site # 14010, Dr. Craig Buettner site # 14004 and Dr. John Schwappach Site # 14045.

We request the following background materials on or before April 10, 2009.

2. Submit the compilation of data listings for use as background material in an upcoming clinical investigator inspection for NDA 22-406, Xarelto. The data listings should include the following parameters:

- Primary efficacy endpoint
- Secondary efficacy endpoint
- Concomitant medications
- Adverse events
- Withdrawals
- Deaths
- Serious Adverse Events
- Protocol violations/deviations
- Randomization list for the site
- Laboratory values (biochemistry, hematology, coagulation parameters, etc.)

The data listings requested are for the following investigators: John Ward, M.D., RECORD 4, Site U.S. 14010; Craig Buettner, M.D. RECORD 4, U.S. Site # 14004 ; and John Schwappach, RECORD 4, U.S. Site #14045.

For each parameter listed in the bullets above, the file should contain a listing of each patient enrolled by that investigator with the pertinent data - e.g., "Primary efficacy endpoint" should contain a listing of Patient 1, 2, 3, 4, etc. with the appropriate outcome of the primary efficacy endpoint.

If you have any questions please feel free to contact me.

ırcus Cato, M.B.A.
ıegulatory Project Management
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(301) 796-2050 (phone)
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Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
nt: Wednesday, March 11, 2009 2:08 PM
: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

Regarding the number of deaths in the enoxaparin group in RECORD studies, explain the inconsistency noted between the individual study reports and the integrated analysis. A total of 25 deaths in the enoxaparin group in all RECORD studies were observed, 15 deaths were included in the primary efficacy analysis (treatment period) and 10 deaths in the follow-up. However, your integrated efficacy analysis, showed a total of 16 deaths in the enoxaparin group. It is also noted that a death at Day 151 in the enoxaparin group was included in the RECORD 4 study, explain the reason to include this patient.

If you have any questions please feel free to contact me.

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.arcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Tuesday, March 10, 2009 9:21 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

Integrated Analyses of Symptomatic VTE and death in RECORD 1-4

Please provide the dataset containing the following variables for the integrated analyses of RECORD 1-4

1 Study Number (Record 1=1, Record 2=2, Record 3=3, Record 4=4)
2 Unique Patient ID
3 Treatment Group (1=Rivaroxaban, 2=Enoxaparin)
4 Treatment Duration (Number of days)
5 Dose per day
6 Total Dose
7 Time to First Symptomatic VTE or Death
8 Censoring status for First Symptomatic VTE or Death (1 = censored, 2 = event)
9 Time to Death
10 Censoring Status for Death (1 = censored, 2 = event)
11 Age (continuous)
12 Gender (1=Male, 2=Female)
13 Race
14 Duration of Surgery (1= (<2h), 2= (>=2h))
15 Any VTE Risk Factor (1=No, 2=Yes)
16 Time to discontinuation
17 Reason for discontinuation
18 Time-To-First-Event for Major Bleeding (treatment duration)
19 Censored Status for Major Bleeding Event (1=Yes, 2=No)
20 Time-To-First-Event for Major Bleeding combined with surgical site (treatment duration)
21> Censored Status for Major Bleeding combined with surgical site (1=Yes,2=No)
22> Time-To-First-Event for Major or clinically relevant Non-Major Bleeding (treatment duration)
23> Censored Status for Major or clinically relevant non-Major Bleeding (1=Yes, 2=No)
24> Time –To-First-Event for Any Bleeding Event (Treatment Duration)
25> Censored Status for Any Bleeding Event (1=Yes, 2=No)

If you have any questions please feel free to contact me.

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Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
nt: Friday, March 06, 2009 12:20 PM
o: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

For 2 subjects (#220134004 and #400013004) who had ALT >3xULN Concurrent With TB >2xULN in ongoing EINSTEIN DVT/PE study, provide complete patient narratives with any available follow-up information, hospital summaries, and assessment by the liver advisory panel if available.

If you have any questions please feel free to contact me.

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Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
nt: Wednesday, March 04, 2009 4:15 PM
o: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Attachments: coverletter.pdf; fda-ir-response-13-feb-2009.pdf

Dear Andrea,

The submitted pooled incidence rates (see attached) for creatinine/urea abnormalities do not match the numbers in ISS Table 1-25 (THR) and 1-26 (TKR) for the pooled treatment-emergent incidence rates. We are looking for the treatment-emergent incidence rate as Table 1-25 and 1-26 but with more categories in creatinine/urea abnormalities.


coverletter.pdf (123 KB)


fda-ir-response-13-feb-2009.pd...

If you have any questions please feel free to contact me.

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9 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, March 04, 2009 11:22 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Importance: High

Dear Andrea,

We request that you submit the following information as soon as possible.

Based on the submitted datasets for ROCKET-AF study, 3 additional cases (#101013, #106065, and #100792) of ALT>3xULN either concurrent or preceding total bilirubin values >2xULN were identified which were not included in your 6-month safety update. Please provide explanation, verify the lab values, and submit the patient clinical narratives.

In addition, one case (#101573) of ALT>3xULN non-concurrent with total bilirubin>2xULN was found in the dataset for the ROCKET study. Please verify the lab values and submit the patient clinical narrative.

If you have any questions please feel free to contact me.

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Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
ent: Thursday, February 26, 2009 9:30 AM
o: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Attachments: N22406 drug dosing modification in pts with and without elevated ALT 022509.doc

Dear Andrea,

We request that you populate the attached table.

N22406 drug dosing modificatio...

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
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	RECORD 1 (N=)		RECORD 2		RECORD 3		RECORD 4		RECORD 1-4	
	Rivaroxaban (N=)	Enoxaparin (N=)	rivaroxaban (N=)	Enoxaparin (N=)	rivaroxaban (N=)	enoxaparin (N=)	rivaroxaban (N=)	Enoxaparin (N=)	rivaroxaban (N=)	Enoxaparin (N=)
# subjects with ALT>3xULN at any time after receiving study drug										
Discontinued prematurely for any reason										
Completed study but had dose/ missed/ held/ decreased										
# subjects with no ALT>3x ULN at any time after receiving study drug										
Discontinued prematurely for any reason										
Completed study but had dose/ missed/ held/ decreased										

Cato, Marcus

From: Cato, Marcus
Sent: Friday, February 20, 2009 11:35 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 (Clinical Pharmacology) information request

Importance: High

Dear Andrea,

We request that you submit the following information within 10 business days.

1)
Based on your mass balance study, you report that M2 related metabolites and M8/9 related metabolites account for approximately 27% and 3.7% of total rivaroxaban dose respectively, when 10 mg 14C rivaroxaban is administered orally to healthy volunteers.

Based on your in vitro studies, you report that CYP2J2 and to a less extent CYP3A metabolize rivaroxaban to M2; CYP3A metabolizes parent to M9. In HLM, both M2 and M9 formations are inhibited by ketoconazole and ritonavir. In rCYP experiments, you concluded that CYP2J2 is the high affinity isoform for the formation of M2. You further conclude that 18% and 14% contributions from CYP3A and CYP2J2 respectively. It appears that this conclusion is based on an assumption that M2 formation (and related M1, M5, 6) is equally contributed by CYP3A (page 182 of your summary 2.7.2 Summary of Clinical Pharmacology Studies). Please provide additional justification to support this assumption. If this assumption is based on your estimated total P450 content by CYP2J2 and CYP3A4 are 1-2% and 30% (an approximately 1:30 ratio), please provide justification for this estimation. Also please address the potential effect of extra hepatic CYP2J2 on the metabolism of rivaroxaban.

2)
Please identify the patients used to create table 14.3.1/15.2.8.1 "Incidence of Treatment-Emergent Major or Non-Major Clin. Relevant Bleeding (Central Adjudication) Stratified By Calc. Creatinine Clearance (4 Categories)-Population: Subjects Valid For Safety Analysis Pool of SN 11354 (Record 1), SN 11355 (Record 4), 11356 (Record 3) and 11357 (Record 2)" found in the "Integrated Analysis of Rivaroxaban (BAY 59-7939) Studies 11354 (Record 1), 11355 (Record 4), 11356 (Record 3) And 11357 (Record 2) With Regard To Efficacy And Safety" pages 1857-58. An electronic data set (SAS transfer format) containing the unique patient identifier, study number, treatment group, event (Y/N), and Clcr group would be sufficient.

If you have any questions please feel free to contact me.

Marcus Cato, M.B.A.
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Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Tuesday, February 17, 2009 11:17 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request: regarding Xarelto lab datasets submitted 30JAN09

Dear Andrea,

We request that you address the following as soon as possible.

- Please clarify the data cut-off dates for ongoing studies for which lab datasets were submitted, and provide a brief statement of how the cut-off dates were decided and implemented.

- Please calculate mean duration of blinded study drug exposure at time of data cut-off for three ongoing studies for which laboratory datasets were submitted:
    - J-ROCKET-AF, (12620)
    - EINSTEIN DVT/PE, (11702)
    - ROCKET-AF, (11630)

- A quick evaluation of the data associated with Study 12620jrocket shows that this study includes a total of 1,185 subjects with a single treatment arm labeled BLINDED and coded 9999. Since there was more than one treatment arm in this study, please re-code the treatments using as an example the ROCKET study where the treatment arms are labeled DUMMY_A and DUMMY_B.

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
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Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
nt: Friday, February 13, 2009 12:37 PM
o: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 Rivaroxaban information request

Attachments: nda22-406-creatinine-request-table.doc

Dear Andrea,

We request that you fill the attached table regarding the incidence of creatinine/urea abnormalities and renal impairment in RECORD studies as soon as possible.

nda22-406-creatini
ne-request-t...

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
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Incidence of Post-Baseline Creatinine and Urea Abnormalities in Pooled RECORD studies

Creatinine/Urea Abnormalities	Rivaroxaban	Enoxaparin
Creatinine		
>1 x ULN		
>1.5 x ULN		
>2 x ULN		
>2.5 x ULN		
>3 x ULN		
Urea		
>1 x ULN		
>1.5 x ULN		
>2 x ULN		
>2.5 x ULN		
>3 x ULN		

Incidence of Post-Day 1 Creatinine and Urea Abnormalities in Pooled RECORD studies

Creatinine/Urea Abnormalities	Rivaroxaban	Enoxaparin
Creatinine		
>1 x ULN		
>1.5 x ULN		
>2 x ULN		
>2.5 x ULN		
>3 x ULN		
Urea		
>1 x ULN		
>1.5 x ULN		
>2 x ULN		
>2.5 x ULN		
>3 x ULN		

Incidence of Post-baseline Renal Impairment Based on Estimated Creatinine Clearance Rate Using Cockcroft-Gault formula
in Pooled RECORD studies

Creatinine clearance ($mL/min/1.73m^2$)	Rivaroxaban	Enoxaparin
60 to 89		
30 to 59		
15 to 29		
<15		

Incidence of Post-Day 1 Renal Impairment Based on Estimated Creatinine Clearance Rate Using Cockcroft-Gault formula
in Pooled RECORD studies

Creatinine clearance ($mL/min/1.73m^2$)	Rivaroxaban	Enoxaparin
60 to 89		
30 to 59		
15 to 29		
<15		

Cato, Marcus

From: Cato, Marcus
ent: Friday, February 13, 2009 11:59 AM
o: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

1. Provide a summary of the number of subjects with elevated liver enzymes at baseline (at Day 0) in RECORD studies.

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
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Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Friday, February 06, 2009 7:36 AM
To: 'Kollath, Andrea [PRDUS]'
Subject: Rivaroxaban letter from DSMB

Attachments: coverletter.pdf; feinbloom-bauer-fda.pdf

Hi Andrea,

Below is your electronic submission dated 2/2/09 (IND 64,892 S1362). The letter (b) (4) mentioned a DSMB report of a death due to liver failure.

Please clarify this case and submit the DSMB report.

Thanks.


coverletter.pdf (93 KB)


feinbloom-bauer-fda.pdf (20 KB...

Marcus Cato, M.B.A.
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4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, January 28, 2009 12:47 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

1. For subject 11702-16018-1005, submit echocardiography reports with clarification of the date (December 1996 or December 2006) and transthoracic echocardiography reports from 1/15/08 to 1/21/08.

2. Provide a summary of outcomes for subjects with ALT>3 xULN for both treatment groups in RECORD studies.

Thanks.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
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(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Wednesday, January 21, 2009 4:08 PM
To: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 Additional information request

Importance: High

Dear Andrea,

We request that you submit the following clinical information on or before Friday January 23, 2009.

1. For subject 16018-1005 in ongoing study, provide hospital summaries and full autopsy report.
2. Provide summary of Liver Advisory Panel assessment for other cases with increased ALT in RECORD studies (exclude those with ALT >3 x ULN concurrent with TB>2xULN).

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
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Office of Oncology Drug Products
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(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
ent: Wednesday, January 21, 2009 3:53 PM
o: 'Kollath, Andrea [PRDUS]'
Subject: NDA 22-406 information request

Importance: High

Dear Andrea,

We request that you submit the following clinical information on or before Friday January 23, 2009.

1. For subject 11354-300014007, provide all local and central LFT results including Day 65 and after (not in narrative).

2. For subject 11355-60009-5028, provide LFT data after Day 55 and any additional follow-up information regarding clinical adverse events.

3. For subject 11357-55003-7007, provide hospital summary, all relevant hepatitis and other serology test results.

4. Provide summary tables as Table 1-2 [Pooled Incidence Rates of Liver-related Postbaseline Laboratory Abnormalities – After Day 0 Baseline (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)] under ISLS by race (White, Asian, and others as separate tables).

5. For subject 10944-84008, provide hospital summary, liver histological assessment by (b) (4) LFT result link and figure of LFT values over time (similar to LFT figures for other subjects).

6. For adjudicated cardiovascular events that occurred off-treatment, list the days relative to the last dose of active treatment for each event for both treatment group.

7. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 1-11 [Incidence of Postbaseline Hepatic Disorder Adverse Events (Subjects Valid for Safety in Pooled RECORD 1-4 Studies)] for subjects under the following categories:
   - MSSO: Cholestasis and jaundice of hepatic origin
   - MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
   - MSSO: Hepatitis, non-infectious
   - MSSO: liver infections
   - MSSO: Possible liver-related coagulation and bleeding disturbances

8. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 2-7 [Incidence of Treatment-Emergent Adverse Events in the MSSO Search Category 'Hepatic Disorders' in Phase 2 Orthopedic Prophylaxis Studies in Venous Thromboembolism (Subjects Valid for Safety in Studies 10942, 10944, 10945, and 11527)] for subjects under the following categories:
   - MSSO: Cholestasis and jaundice of hepatic origin
   - MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
   - MSSO: Possible liver-related coagulation and bleeding disturbances

9. For hepatic adverse events, provide patient narratives with CRF link and LFT result link for Table 2-14 [Incidence of Treatment-emergent Adverse Events for "Hepatic Disorders" in Phase 2 Treatment Studies

in Venous Thromboembolism (Subjects Valid for Safety in Studies 11223 and 11528)] for subjects under the following categories:

- MSSO: Cholestasis and jaundice of hepatic origin
- MSSO: Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
- MSSO: Liver infections
- MSSO: **Liver neoplasms, benign**

If you have any question please feel free to contact me.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

Cato, Marcus

From: Cato, Marcus
Sent: Monday, January 12, 2009 12:25 PM
To: 'Kollath, Andrea [PRDUS]'
Cc: Leaman, Diane V
Subject: NDA 22-406 information request

Dear Andrea,

We request that you submit the following information as soon as possible.

1. For subject 11355-140165153 who died of fatal bleeding, provide full autopsy report, hospital summary, lab data including LFTs and coagulation tests during the treatment and in hospital before death, and investigator assessment for the event.

2. Clarify the number of cardiovascular events in RECORD trials. The discrepancy is noted in the number of events between the individual RECORD study reports and ISS report (Table 1-22).

3. Provide summary of number of patients with maximum ALT>3 ULN and maximum TB>2 ULN (not concurrent) for all completed studies and provide link to narrative and CRF. Also provide this information for ongoing studies if available.

Thanks.

Marcus Cato, M.B.A.
Regulatory Project Management
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
(301) 796-2050 (phone)
(301) 796-9849 (fax)
Marcus.Cato@fda.hhs.gov

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/s/

Marcus Cato
4/14/2009 07:49:06 PM
CSO

Marcus Cato
4/14/2009 07:49:17 PM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
DDMAC: c/o Michelle Safarik

FROM: Diane Leaman, SRPM, Division of Medical Imaging and Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 16, 2008		NDA 22-406	NDA	July 28, 2008

NAME OF DRUG	PRIORITY CONSIDERATIONS	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xarelto (Rivaroxaban) tablsts	Standard	Anti Xa	February 9, 2008

NAME OF FIRM: Johnson and Johnson

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please see attached sponsor's draft original package insert labeling for Xarelto™ (Rivaroxaban) tablets for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement surgery or knee replacement surgery. Please provide review and attend labeling meetings as part of review team. Labeling is in EDR at \\CDSESUB1\EVSPROD\NDA022406\0000.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

6 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Diane V Leaman
12/17/2008 09:13:27 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406 **INFORMATION REQUEST LETTER**

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 25, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to your submission dated July 25, 2008.

We are reviewing the Clinical section of your submission and have the following comments and information requests. We request a written response in 30 days in order to continue our evaluation of your NDA.

1. Safety Data Request: Laboratory Data Relevant To Drug- Induced Liver Injury In All Completed And Ongoing Clinical Trials With Rivaroxaban

   Analysis Datasets to be submitted consistent with the CDISC Standard:

   Please provide complete laboratory test results (including lab test results obtained from central ***as well as*** local laboratories) for subjects during all Phases 1-4 completed and ongoing clinical trials with rivaroxaban, for the following laboratory tests: ALT (serum alanine aminotransferase), AST (serum aspartate aminotransferase), GGT (gamma glutamyl transferase), TBL (total serum bilirubin concentration), DIR (direct bilirubin concentration), ALP (alkaline phosphatase), and INR (international normalized ratio).

   Please include in this dataset all results for specified lab tests obtained at any time after initiation of study therapy, or within 30 days after discontinuation of study therapy, regardless of whether the test was specified per protocol.

   Please carefully organize your data, including reference ranges, and provide the following data sets consistent with the CDISC standard as SAS transport files:

   a. Liver data set: This data set should include the patients' liver-test results observed over time. The data thus collected should have multiple records per patient.

   b. Patient demographic data set: This data set should include selected patients' characteristics, such as the date of birth, race, sex, etc. The data thus collected should

have a single record per patient for the patients' characteristics do not change over time during the clinical study.

c. Patient narrative data set: This data set should include the narratives based on CRF and including physician's remarks. Each patient should have a single record consisting of a paragraph in plain text.

Formats for the data sets, above, are specified as follows.

1) Liver data format specification

Requirement	Variable name	The variable means...	Variable-type
1. Required	STUDYID	Unique identifier for a study within the submission	Char
2. Required	USUBJID	Unique subject identifier within the submission	Char
3. Required	TRTCD	Treatment Code	Num
4. Required	TRTGRP	Treatment Group	Char
5. Required	EXSTDT	Start Date of Dose	Num (ISO 8601 YYYY-MM-DD)
6. Required	EXDT	Date of Exam	Num (ISO 8601 YYYY-MM-DD)
7. Required	ONPROTOCOL	Is the subject on protocol at the time of exam (Y/N)	Char
8. Required	EXENDT	End Date of Dose	Num (ISO 8601 YYYY-MM-DD)
9. Required	ONPROTOCOL		
10. Required	ALT	Serum alanine aminotransferase activity (U/L)	Num
11. Required	ALT_REF_HIGH	ALT High Normal Range (U/L)	Num
12. Required	BILI	Total serum bilirubin concentration (mg/dL)	Num
13. Required	BILI_REF_HIGH	BILI High Normal Range (mg/dL)	Num
14. Required	AST	Serum aspartate aminotransferase (U/L)	Num
15. Required	AST_REF_HIGH	AST High Normal Range (U/L)	Num
16. Required	ALP	Alkaline phosphatase (U/L)	Num
17. Required	ALP_REF_HIGH	ALP High Normal Range (U/L)	Num
18. Optional	INR	International Normalized Ratio	Num
19. Optional	GGT	Gamma glutamyl transferase	Num
20. Optional	BILIDIRECT	Direct-reacting serum bilirubin (mg/dL)	Num

2) Patient demographic data format specification

Requirement	Variable name	The variable means...	Variable-type
1. Required	STUDYID	Unique identifier for a study within the submission	Char
2. Required	USUBJID	Unique subject identifier within the submission	Char
3. Required	INVID	Investigator Identifier	Char
4. Optional	INVNAM	Investigator Name	Char
5. Optional	INVDESC	Investigator Description	Char
6. Required	BIRTHDT	Date of birth	Num (ISO 8601 YYYY-MM-DD)
7. Required	SEX	Sex	Char
8. Optional	RACE	Race	Char
9. Optional	COUNTRY	Country	Char

Requirement	Variable name	The variable means...	Variable-type
10. Required	HEIGHT	Height in Centimeters	Char
11. Required	WEIGHT	Weight in Kilograms	Char
12. Required	COMPLETE	Did the subject complete the study (Y/N)	Char
13. Required	DROPOUTDATE	Date of discontinuation, if applied	Num (ISO 8601 YYYY-MM-DD)
14. Required	DROPOUTREASON	Reason for discontinuation, if applied	Char

3) Patient narrative data format specification

Requirement	Variable name	The variable means...	Variable-type
1. Required	STUDYID	Unique identifier for a study within the submission	Char
2. Required	USUBJID	Unique subject identifier within the submission	Char
3. Required	NARRATIVE	Patient's narrative consisting of a paragraph in plain text.	Char

It is not necessary to include all subjects in this patient narrative data set. However, please be sure to include narratives for all subjects with ***any*** of the following conditions:

- ALT≥5xULN,
- TBL≥2xULN,
- Death;
- Discontinuation of study drug after an elevation of serum transaminase or bilirubin.

Individual clinical narratives should include the following information:

- Medical history and concomitant medications;
- Identification of treatment group / study drug (if unblinded);
- Dose, indication, duration of study therapy in days;
- Subject's medical history and concomitant medications;
- Dates and laboratory values for ALT, AST, total bilirubin, serology, and any other diagnostic tests done to evaluate liver disease including X-ray, ultrasound, or liver biopsy;
- Clinical course of any signs or symptoms of liver disease, including jaundice;
- Differential diagnosis and final diagnosis of liver disease;
- Study site investigator, Company, and/or Liver Advisory Board assessment of relationship of study drug to abnormal hepatobiliary lab results or adverse events;
- Clinical course of liver-related adverse events including treatment and outcome;
- For deaths, please provide a link to autopsy results/report, if feasible.
- Complete information about the resolution, or progression, of increased ALT or total bilirubin in each of these study subjects, including time to complete resolution of all hepatobiliary lab results, or most current available patient status for any cases in which the events had not resolved at the time of report preparation. Please include any

hepatitis serology data and any other data relevant to the clinical course of the patient in the trial.

2. Descriptive Statistics Request: Number and Percent of Study Subjects with ALT (Alanine Aminotransferase) and TBL (Total Bilirubin) in Specified Categories

Populate the following tables with relevant numbers of study subjects from all completed and ongoing (blinded) Phases 1-4 clinical trials with rivaroxaban, using the liver data you submitted to the FDA. Use the row totals to calculate the percentages. Do not combine studies when producing the following tables.

Number (%) of rivaroxaban-treated subjects with maximal TBL by maximal ALT: All completed clinical studies regardless of indication or study duration (includes central + local laboratory data)						
	Maximal TBL (xULN)					
Maximal ALT	0 – 1	>1 – 2	> 2 – 2.5	>2.5 – 3	>3	Total
≤1 xULN						
>1-2 xULN						
>2-3 xULN						
>3-5 xULN						
>5-10 xULN						
>10 xULN						
Total						

Number (%) of comparator-treated subjects with maximal TBL by maximal ALT: All completed clinical studies regardless of indication or study duration (includes central + local laboratory data)						
	Maximal TBL (xULN)					
Maximal ALT	0 – 1	>1 – 2	> 2 – 2.5	>2.5 – 3	>3	Total
≤1 xULN						
>1-2 xULN						
>2-3 xULN						
>3-5 xULN						
>5-10 xULN						
>10 xULN						
Total						

Produce the same tables for ongoing studies in the same fashion.

If you have any questions, call Diane Leaman, Safety Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Kyong Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Kyong Kang
12/12/2008 02:43:29 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406 **INFORMATION REQUEST LETTER**

Johnson and Johnson Pharmaceutical Research and Development
Attention: Andrea F. Kollath, DVM
Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Kollath:

Please refer to your July 28, 2008 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) tablets.

We also refer to your submission dated November 25, 2008.

We are reviewing the Statistical, Chemistry, Manufacturing and Controls and Clinical Pharmacology sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Chemistry, Manufacturing and Quality Control

1. Please submit a copy of your change control protocol for the drug product or an abbreviated version or summary that demonstrates the process.

Statistics

2. Please submit the following data sets (to facilitate these requests, you may request us to arrange a telephone conversation between our statistical team and your representatives):

   a. Time-to-first event (including treatment phase and follow-up) for major bleeding, major bleeding including surgical site, and major or non-major clinically relevant bleeding.

   b. We suggest that you use a survival analysis for multiple bleeding events as well. Therefore, submit bleeding data in the multiple event setting. That is, include the starting day of the event and the stopping day of the event in the date-frame.

Clinical Pharmacology

3. We are particularly concerned about the safety and efficacy of Rivaroxaban in certain patients. Specifically, our preliminary review of your application suggests a need for a lower strength tablet or a scored 10 mg tablet of Rivaroxaban to allow for downward dose adjustment in patients with renal impairment, hepatic impairment, and/or concurrent use of a moderate or strong CYP3A4 inhibitor. FDA's preliminary analysis suggests that increasing the dosing interval is not a viable option in these patients. Without downward dose adjustment, a significant part of the target population will not be able to utilize Rivaroxaban and inappropriate use of the current strength in these populations could pose an unacceptable risk. We recommend you to develop a lower strength tablet or a scored 10 mg tablet of Rivaroxaban and provide adequate data to support bioequivalence to the current proposed dose. We encourage you to promptly obtain this information and supply it as an amendment to your application. We ask that you comment upon this request within ten business days. Within your comment, specifically address your ability to supply the information in sufficient time to allow us to review it within this review cycle.

4. A preliminary review of your application indicates there is an approximately 40% higher exposure of Rivaroxaban in Japanese subjects compared to other ethnic groups. We note your assertion that this is related to body weight; however, our preliminary analysis of your population-pharmacokinetic (Pop-PK) data does not suggest this to be the case. We note that age was a significant covariate. Given the results of our preliminary analysis, we ask you to provide an additional explanation for the higher exposure in the Japanese population. Pharmacogenetic differences should be considered, in addition to other factors, in your response. We ask that you submit a response to this request within ten business days.

If you have any questions, call Diane Leaman, Regulatory Health Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Rafel (Dwaine) Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

12/5/2008 05:15:25 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 4, 2008

TO: File

FROM: Diane Leaman, SRPM

SUBJECT: **Xarelto Mid-Cycle Review**
NDA 22-406, Xarelto (rivaroxaban) tablets

The midcycle review for Xarelto™ (Rivaroxaban) tablets was held at 10:00 AM on December 2, 2008 at the FDA White Oak campus in Building 22, Conference Room 1415.

Those in attendance are as follows:

Richard Pazdur, Office Director, Office of Oncology Drug Products
Kathy Robie-Suh, M.D., Ph.D., Clinical Team Leader, Division of Medical Imaging and Hematology Products (DMIHP)
Min Lu, M.D., Medical Officer, DMIHP
Diane Leaman, Safety Regulatory Project Manager, DMIHP
Marcus Cato, Regulatory Project Manager, DMIHP
Yash Chopra, M.D., Ph.D., Pharmacologist, DMIHP
Dr. Eldon Leutzinger, Ph.D., Pre-Marketing Assessment Leader, Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V
Aloka Chakravarty, Ph.D., Director, OTS/OB/Division of Biometrics V
Chava Zibman, Staff Fellow, OTS/Office of Biostatistics
Jyoti Zalkikar, Ph.D., Statistical Team Leader
Satish Misra, Ph.D., Statistical Reviewer
Qing Xu, Ph.D., Statistical Reviewer
Nam Atiqur (Atik) Rahman, Ph.D., acting Deputy Director, Office of Translational Science (OTS), Division of Clinical Pharmacology 5, (DCP5)
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Ph.D., Biopharmaceutics Reviewer
Raj Madabushi, Ph.D., OCP, Clinical Pharmacology Reviewer
Rosane Charlab Orbach, Staff Fellow, OTS/Office of Clinical Pharmacology (OCP)

The following presentations were made:

"NDA 22-406 Xarelto Tablets (Rivaroxaban) Mid-Cycle Review (CMC)" by Josephine Jee, presented by Eldon Leutzinger.
"Xarelto (NDA 22-406) Rivaroxiban IR Tablets Mid-cycle Meeting" by Joseph A. Grillo, Pharm,D., CP Reviewer
"Preclinical Midcycle Review" by Yash Chopra
"MidCycle Meeting December 2, 2008 Statistics" by Qing Xu, Ph.D.
"Xarelto (Rivaroxaban) NDA 22-406 Mid-Cycle Presentation" by Min Lu, M.D., M.P.H.

Action Items:

Statistics: Statistics will request an analysis from the sponsor to analyze recurrent bleeding events to see if there is a significant difference between the proximal and distal DVT in the studies.

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/s/

Diane V Leaman
12/15/2008 09:17:43 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

Johnson and Johnson Pharmaceutical Research and Development LLC
Attention: Andrea F. Kollath
DVM Director, Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear M. Kollath:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xarelto™ (Rivaroxaban) Tablets

We also refer to the meeting between representatives of your firm and the FDA on November 17, 2008. The purpose of the meeting was to discuss the needed Chemistry, Manufacturing and Control items to be included in the NDA 22-406.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Regulatory Project Manager,
Division of Medical Imaging and
Hematology
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 17, 2008
TIME: 2:30 PM – 4:00 PM
LOCATION: White Oak, Bldg 22, Room 1313
APPLICATION: NDA 22-406
DRUG NAME: Xarelto™ (rivaroxaban) Tablets
TYPE OF MEETING: NDA Orientation

MEETING CHAIR: Dr. Rafel Rieves

MEETING RECORDER: Diane Leaman

FDA ATTENDEES:

Office of Oncology Drug Products/Division of Medical Imaging and Hematology Products (DMIHP)

Diane Leaman, Safety Regulatory Health Project Manager

Office of Pharmaceutical Science, Office of New Drug Quality Assurance,
Richard Lostritto, Ph.D., Head, Division Pre-Marketing Assessment III and Manufacturing Science (DPAMS)

Division of Pre-Marketing Assessment and Manufacturing Science, Branch V
Eldon Leutzinger, Ph.D., Premarketing Assessment Lead
Josephine Jee, Ph.D., Chemistry Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Johnson and Johnson Pharmaceutical Research and Development LLC (J&J)

Nancy Micalizzi, Chemistry, Manufacturing and Controls
Donald Doyle, Chemistry, Manufacturing and Controls
Sanjay Jalota, Regulatory Global Regulatory Lead, Regulatory Affairs
Andrea Kollath, Regulatory Affairs

Bayer HealthCare (Bayer)

Larry Winick, M.A., Deputy Director U.S. Regulatory Affairs
Robert Kelly, Chemistry, Manufacturing and Controls
Stephen Bartel, Chemistry, Manufacturing and Controls

BACKGROUND:

On July 28, 2008, J&J submitted NDA 22-406. On October 9, 2008, the Agency sent J&J and telefacsimile requesting the following information for NDA 22-406:

Information on the Drug Substance

1. Nomenclature

2. Description
3. Molecular Structure, Molecular Weight and Molecular Formula
4. Physicochemical Properties
5. Specifications (Release and Stability, if different)
6. Stability Protocol and Stability Commitment
7. Stability Data

Information on the Drug Product

1. Description
2. Drug Components and Composition
3. Specifications (Release and Stability, if different)
4. Stability Protocol and Stability Commitment
5. Stability Data
6. Container Closure
7. Container and Carton Labels
8. Environmental Assessment

The Agency also requested the sponsor to implement a Change Control Protocol.

MEETING OBJECTIVES:

To clarify the additional Chemistry, Manufacturing and Control (CMC) information needed in regard to the CMC portion of the Xarelto NDA and to discuss the change control procedures for the NDA.

DISCUSSION POINTS:

In Module 1., the Agency finds that the information in the NDA is elaborate and is concerned that the information that is currently found in Module 1. is merely a list of items in the DMFs. The Agency needs the specific information on the drug product available in the NDA. We need to know that you, as sponsor of the NDA, know what the product is and if the product is changed and if it is living up to specifications.

The sponsor responded that the Reviewer's Guide provided information in the three DMFs.

The Agency clarified that the adequacy of the information in the NDA is a review issue. There is a dearth of CMC information in the NDA. The NDA does not indicate what you, as sponsor, would do if the product becomes out of specification. What change controls do you have? Do you know what is going on? The sponsor said that the change control procedure is at the manufacturing site and that the control is done at inspection. The Agency argued that batch specifications for the drug product need to be placed in the NDA. J&J explained that the reason for having three DMFs is because there are two companies involved with the manufacturing process of the product (J&J and Bayer) and two DMFs are held by one company and the other DMF is held by the other company. J&J further noted that Bayer developed the compound and that Bayer is also an alternate manufacturer of the product. The two companies had a co-development agreement. Both companies DMFs support the required suppliers.

The Agency noted that we have accepted the "process" of submitting several DMFs into an NDA. However, this is a review issue. Multiple DMFS in a submission is acceptable, however,

the sponsor needs to be able to do what the NDA purports the sponsor to do. If there is a gap between the drug owner and the DMF holder, the sponsor needs to know about it. The sponsor is the responsible party. A DMF can be changed at any time. As the sponsor, you can seek drug changes with a DMF. A DMF does not need prior approval to make changes. As NDA sponsor, you need an iron-clad system. Any change has to have proper regulatory oversight. Any change must come from the NDA holder.

The NDA is a link to the CMC information. Access to the CMC information would be unwieldy technically on our end after approval of an NDA that does not contain the necessary information. If there are batches of the product that are out of specification, we need to be able to find the proper information in the NDA to prevent review issues and unfavorable actions in the future. We need a modicum of information in the NDA to ensure the review process.

The sponsor confirmed that the information referenced in Module 3, and previously requested (above) will be submitted to the NDA.

The sponsor will submit Post-approval changes protocol according to 21CFR314 regarding DMF cross reference to the NDA.

Johnson and Johnson and Bayer noted that the Agency request sounds acceptable.

DECISIONS (AGREEMENTS) REACHED:

The Agency minutes will be the final/official minutes of the meeting.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

The sponsor will submit the requested information to the NDA.

ATTACHMENTS/HANDOUTS:

None.

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/s/

Diane V Leaman
12/1/2008 11:26:27 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 1, 2008

TO: File

FROM: Diane Leaman

SUBJECT: **November 26, 2008 e-mail and e-mail stream regarding Clinical information request.**

NDA 22-406, Xarelto (rivaroxaban) tablets

Hi Diane,
Thank you the clarification.
We will get started on these.
Happy Thanksgiving!!
Best regards,
Andrea
-----Original Message-----
From: Leaman, Diane V [mailto:diane.leaman@fda.hhs.gov]
Sent: Wednesday, November 26, 2008 9:20 AM
To: Kollath, Andrea [PRDUS]
Cc: sanjay.jalota@its.jnj.com
Subject: RE: NDA 22-406 Xarelto

Andrea,

A list with patient identifier hyperlinked to the CRFs should be fine. If this does not work for us, then, maybe we can look at doing the leaf element.

One thing that you can clarify is the location of the liver data in the CRFs. (when we open the CRF, we do not see the liver values). We want to be sure we can see the CRFs with the data from patients who had ALT > 3 and bilirubins >2. Was there a central laboratory where liver function tests were done? A sampling time is noted, but not the lab values.

For ongoing studies, data should not be unblinded for purposes of satisfying this request (where data are already unblinded, e.g., due to intervention for AE, the SAE data can be presented with the treatment that is known). Please take great care to proceed in responding to our request in such a manner that the integrity of the ongoing efficacy trials is not in any way compromised.

We also want the original, full autopsy results for all death cases, especially Hy's law cases.

I hope this helps you obtain our requests.

In addition, I checked with the CMC group and they want a copy of the change control protocol, if it is not already part of the CMC submission you just sent. If it is too unwieldy for an eCTD submission, you could send us a summary or synopses/overview of the protocol to give us assurance that something is in place for this aspect of the NDA.

Diane

From: Kollath, Andrea [PRDUS] [mailto:AKollath@its.jnj.com]
Sent: Tuesday, November 18, 2008 5:15 PM
To: Leaman, Diane V
Subject: RE: NDA 22-406 Xarelto

Hi Diane,
I will get back to you as to when we can send this.
Kind regards,
Andrea

-----Original Message-----
From: Leaman, Diane V [mailto:diane.leaman@fda.hhs.gov]
Sent: Tuesday, November 18, 2008 3:48 PM
To: Kollath, Andrea [PRDUS]
Subject: NDA 22-406 Xarelto
Importance: High

Andrea,

When we look in our EDR for the CRFs the pdf files appear to be named with the study number followed by a sequential number from 1 to the total number of CRFs. We can't look at the CRF folder and immediately identify which pdf file is for which subject. We have to open each file and look on the CRF to see the actual patient number. It would be nice to have a table that clearly identifies which pdf file goes with which patient.

Please provide us with a table for each study providing patient identifier for each patient listed in the CRF pdf files such as:

1. CRF file patient identifier
11354-crf-1 11354-100014022
11354-crf-2 11354-100014032.

2. A separate folder containing the CRF pdf files for all patients in the database who had peak AST>3xULN and total bilirubin >2xULN and patients who had peak ALT>3xULN and total bilirubin >2xULN. For this folder also provide a table identifying the pdf files as described above.

3. Also, clarify whether you have submitted case report files for patients that potentially meet Hy's law criteria and describe how these patients were treated.

Please also provide:

4. Original CRFs for all subjects who had ALT>3x ULN and TB>2x ULN with all central or local LFTs available based on all database (completed and ongoing studies).

5. Full autopsy reports for patients who died with increased LFT's during or after treatment If autopsy was performed.

Thanks.

Diane Leaman, SRPM
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
12/1/2008 11:11:27 AM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	October 22, 2008
TIME:	3:00 PM - 4:00 PM EST
LOCATION:	CDER WO 2376 conf rm Bldg22
APPLICATION:	NDA 22-406
SPONSOR:	Johnson and Johnson (J&J)
DRUG NAME:	Xarelto™ (Rivaroxaban) Tablets
TYPE OF MEETING:	CMC, Teleconference

MEETING CHAIR: Eldon Leutzinger

MEETING RECORDER: Marcus Cato

FDA ATTENDEES:

Office of Pharmaceutical Science / Office of New Drug Quality Assessment/
Division Of Pre-Marketing Assessment And Manufacturing Science Branch V

Josephine M Jee, Ph.D., CMC Reviewer
Eldon E Leutzinger, Ph.D., Pharmaceutical Assessment Lead

Office of New Drugs/ Office of Oncology Drug Products/
Division of Medical Imaging and Hematology Products

Marcus Cato, M.B.A., Regulatory Health Project Manager
Ebla Ali Ibrahim, M.S., Regulatory Health Project Manager
Florence Moore, M.S., Acting Regulatory Project Management Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Attendees from Johnson & Johnson Pharmaceutical Research and Development

Donald Doyle, ChemPharm Leader
Nancy Micalizzi , CMC Regulatory Affairs
Andrea Kollath, Regulatory Affairs
Kelly Kurtz-Colone, Global Regulatory Dossier Leader

Attendees from BayerHealthCare Pharmaceuticals, Inc.

Robert Kelly, Director, Regulatory Affairs CMC and Marketed Products
Deborah Flint, Associate Director, CMC Regulatory Affairs
Stephan Bartel, Global Regulatory Affairs CMC Manager
Dietmar Boecker, Global Submissions
Larry Winick, Regulatory Affairs
Cesar Vinces, Global Submissions
Gerhard Schlueter, Head of General Medicine and Cardiovascular Regulatory Affairs

BACKGROUND:

NDA 22-406 for Xarelto™ (Rivaroxaban) Tablets was submitted July 28, 2008 (received July 28, 2008) for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement therapy and for patients undergoing knee replacement therapy.

MEETING OBJECTIVES:

To clarify the Agency's CMC requests and discuss how to submit the requested information.

DISCUSSION POINTS:

Johnson and Johnson (J&J) referenced a prior agreement with the agency regarding the acceptability of having the CMC information in a Drug Master File (DMF). FDA responded that it is not acceptable to reference a DMF for drug product data, but it is only acceptable to reference the DMF for drug substance data. FDA also reminded J&J that the code of federal regulations (CFR) also requires certain information at a minimum. J&J referenced the pre-NDA meeting with the agency and stated that this was addressed.

FDA commented that usually a firm bringing a product in from a supplier requires a battery of testing and there is particular concern with J&J having two products from different suppliers. FDA also stated that qualification of the drug product is needed. J&J asked if the drug substance information was acceptable in a DMF. FDA indicated that it was acceptable for the drug substance data to be in a DMF but has more concerns regarding the drug product data being in a DMF.

J&J mentioned that in module one of the application, there is product specification information and a reviewers guide to tie together any differences. FDA responded that this information should have been in module three. FDA agreed to check module one for the aforementioned information and asked the sponsor if all the required information is in module one. J&J stated that all required information was in module one and the DMF. J&J further stated that module one also contains the container and carton labels. FDA agreed to go back to verify if the application contained all the CMC information that is required for a NDA submission.

DECISIONS (AGREEMENTS) REACHED:

None

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Drug product information submission to the NDA verses what can be referenced in a DMF.

ACTION ITEMS:

FDA agreed to check module one of the submission for the aforementioned information and give the sponsor feedback.

ATTACHMENTS/HANDOUTS:

None.

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/s/

Marcus Cato
11/13/2008 03:16:39 PM

Florence Moore
11/25/2008 02:21:17 PM

Dear Andrea,

We have determined there is information regards Chemistry, Manufacturing and Controls for drug substance and drug product that is missing in your application and that is critical for its review. Accordingly, provide the following information:

A. Drug Substance
   1. Nomenclature
   2. Description
   3. Molecular Structure, Molecular Weight and Molecular Formula
   4. Physicochemical Properties
   5. Specifications (Release and Stability, if different)
   6. Stability Protocol and Stability Commitment
   7. Stability Data

B. Drug Product
   1. Description
   2. Drug Components and Composition
   3. Specifications (Release and Stability, if different)
   4. Stability Protocol and Stability Commitment
   5. Stability Data
   6. Container Closure
   7. Container and Carton Labels
   8. Environmental Assessment

We also request that a Change Control Protocol be implemented for covering potential future changes in the manufacturing process for drug substance and drug product, since such changes (if they were to occur) could impact release specifications and ultimately the purity and quality of the drug product. Include the Change Control Protocol along with the other information requested as outlined above.

Since there are two alternate sources of Xarelto™ Tablets, there must be an appropriate mechanism in place to assure that the tablets from all sources used have the same purity and quality. That responsibility is Johnson & Johnson's, and should consist of appropriate monitoring of Xarelto drug substance and drug product for purity and quality, meaning to meet the regulatory specifications (Release and Stability). This is the basis for the requested CMC information.

If you have any questions, call me at (301) 796-1424.

Sincerely,

Diane Leaman, Safety Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
10/9/2008 02:31:25 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-406

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Attention: Andrea F. Kollath
DVM Director, Regulatory Affairs
920 U.S. Highway 202
P.O. Box 300 Raritan, NJ 08869-0602

Dear Ms. Kollath:

Please refer to your new drug application (NDA) dated July 22, 2008, received July 28, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Xarelto™ (Rivaroxaban) Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is May 28, 2009.

During our filing review of your application, we identified the following potential review issues:

The package insert should be revised to be in full compliance with the Physician's Labeling Rule format. Please see preliminary comments below.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We request that you submit the following information:

Please revise your package insert as follows:

A. HIGHLIGHTS section

(b) (4)

2. In the **CONTRAINDICATIONS** section, (b) (4) shorten the bullet to read "Active major bleeding."

3. In the **CONTRAINDICATIONS** section, (b) (4) shorten the bullet (b) (4)

4. (b) (4)

5. In the **USE IN SPECIFIC POPULATIONS** section, delete (b) (4) (b) (4)

(b) (4)

6. In the **USE IN SPECIFIC POPULATIONS** section, in the Renal impairment (8.6) subsection, shorten the bullets and delete all sub-bullets. We recommend the following:

   "Severe Renal Impairment: Use with caution; use with concomitant medications (e.g., strong CYP3A4 inhibitors); may increase Rivaroxaban plasma concentrations
   Kidney failure: Do not use
   Hepatic impairment: Association with coagulopathy; may lead to bleeding (8.7)."

7. In the **PATIENT COUNSELING INFORMATION** section, delete the phrase (b) (4)

B. **FULL PRESCRIBING INFORMATION** section

1. Throughout the labeling refer to Xarelto in title case, not all capital letters.

2. In the **ADVERSE REACTIONS** section, (b) (4) The contents of the current section may need to be placed in another section of the labeling and this subsection may need to be deleted until data after approval of the drug product has been collected. The corresponding section title in the **FULL PRESCRIBING INFORMATION: CONTENTS** should also match the heading to this subsection.

3. In the **DRUG INTERACTIONS** section, revise the title [redacted] to clarify more clearly the specific items in this subsection. The corresponding section title in the **FULL PRESCRIBING INFORMATION: CONTENTS** should also match the heading to this subsection.

4. In the **USE IN SPECIFIC POPULATIONS** section, in the **8.1 Pregnancy** subsection, [redacted] provide an explanation as to why this drug is a Category [redacted] pregnancy drug.

We have also determined that there is information regarding Chemistry, Manufacturing and Controls for the drug substance and drug product that is missing in your application that is critical for its review. Accordingly, provide the following information:

A. Drug Substance

1. Nomenclature
2. Description
3. Molecular Structure, Molecular Weight and Molecular Formula
4. Physiochemical Properties
5. Specifications (release and Stability, if different)
6. Batch Analysis
7. Stability Protocol and Stability Commitment
8. Stability Data

B. Drug Product

1. Description
2. Drug Components and Composition
3. Specifications (Release and Stability, if different)
4. Batch Analysis
5. Stability Protocol and Stability Commitment
6. Stability Data
7. Container Closure
8. Container and Carton Labels
9. Environmental Assessment

We also request that you implement a Change Control Protocol for covering potential future changes in the manufacturing process for the drug substance and drug product, since such changes (if they were to occur) could impact release specifications and ultimately the purity and quality of the drug product. Include the Change Control Protocol along with the other information requested as outlined above.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients less than 18 years of age.

If you have any questions, call Mrs. Diane Leaman, Regulatory Project Manager, at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Rafel Dwaine Rieves, M.D.
Director
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Rafel Rieves

10/1/2008 05:57:17 PM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 18, 2008
TIME: 2:30 PM – 4:00 PM
LOCATION: White Oak, Bldg 22, Room 1313
APPLICATION: NDA 22-406
DRUG NAME: Xarelto™ (rivaroxaban) Tablets
TYPE OF MEETING: NDA Orientation

MEETING CHAIR: Dr. Rafel Rieves

MEETING RECORDER: Mrs. Diane Leaman

FDA ATTENDEES:

Office of Oncology Drug Products

Richard Pazdur, M.D., Director

Division of Medical Imaging and Hematology Products (DMIHP)

Rafel (Dwaine) Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Medical Officer,
Diane Leaman, Safety Regulatory Health Project Manager
Ebla Ali-Ibrahim, Regulatory Health Project Manager

Division of Drug Oncology Products
Ann Farrell, M.D., Deputy Director

Office of Drug Evaluation I

Division of Cardiovascular and Renal Products

Stephen Grant, M.D., Medical Team Leader

Office of Biostatistics/Division of Biometrics V

Jyoti Zalkikar, Ph.D., Statistical Team Leader
Satish Misra, Ph.D., Statistical Reviewer
Qing Xu, Ph.D., Statistical Reviewer

Office of Pharmaceutical Science, Office of New Drug Quality Assurance, Division of Pre-Marketing Assessment and Manufacturing Science, Branch V

Sarah Pope, Ph.D., Branch Chief
Josephine Jee, Ph.D., Chemistry Reviewer

Office of Clinical Pharmacology (OCP)

Joseph Grillo, Pharm.D. Pharmacology Reviewer

Office of Translational Science/Office of Biometrics/Division of Biometrics VI
Mark Levenson, Ph.D., Statistician
Chava Zibman, Ph.D., Statistician, Staff Fellow

Office of Surveillance and Epidemiology

John R. Senior, M.D., Medical Officer (Hepatotoxicity)

EXTERNAL CONSTITUENT ATTENDEES:

Johnson &Johnson

Peter DiBattiste, Therapeutic Area Head Cardiovascular
Gary Peters , Franchise Medical Leader
Leonard Oppenheimer, Statistical Sciences
John Zhang, Statistical Sciences
Juliana Ianus, Statistical Sciences
Debra Karvois, Clinical Project Scientist
Mehul Desai, MD, Clinical
Michael Kronig,MD Regulatory CV Therapeutic Area Head Cardiovascular
An Thyssen, Clinical Pharmacology
Sanjay Jalota, Regulatory Global Regulatory lead
Andrea Kollath, Regulatory Affairs,
Andrea Masciale, Regulatory Affairs, FDA Liaison Office
Sigmond Johnson, Project Management
Bode, Nini, Preclinical
Harry Flanagan, Pharmacovigilance
Dina Anand, Pharmacovigilance
Nancy Micalizzi, CMC

Bayer Healthcare, Inc.

Scott. Berkowitz Franchise Medical Leader
Martin. Homering, Statistical Sciences
Dagmar. Kubitza, Clinical Pharmacology
Alice. Benson Statistical Sciences
Volker. Geiss Preclinical
Andrea. Derix Regulatory Affairs,
Sabine Dittmar, Pharmacovigilance
Torsten.Westermeier, Statistical Sciences
Aasia Bhatti, Pharmacovigilance

BACKGROUND:
NDA 22-406 for Xarelto™ (Rivaroxaban) Tablets was submitted July 28, 2008 (received July 28, 2008) for prophylaxis of deep vein thrombosis and pulmonary embolism in patients undergoing hip replacement therapy and for patients undergoing knee replacement therapy.

MEETING OBJECTIVES:

To provide an avenue for the sponsor to present an overview of the NDA for Xarelto (Rivaroxaban) tablets submitted July 28, 3008. See attached copies of slides presented at the meeting.

ATTACHMENTS/HANDOUTS:

See attached

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/s/

Diane V Leaman

10/9/2008 01:22:28 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: Office of Surveillance and Epidemiology: c/o Dr. John Senior

FROM: Diane Leaman, RPM, Division of Medical Imaging and Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 17, 2008		22,406	NDA	July 22, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xarelto (rivaroxaban) tablets	Standard	Anti-Xa	October 30, 2008

NAME OF FIRM: Johnson and Johnson Pharmaceutical Research and Development, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- X LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review data related to liver toxicity. This NDA is submitted for Xarelto (rivaroxaban), an oral anticoagulant for the prophylaxis of deep vein thrombosis and Pulmonary embolism in patients udnergoing hip replacement sruger or knee replacement surgery. Though this NDA is for short-term use of Xarelto, the drug is also being studied for a chronic use (stroke preventionin atrial fibrillation). The NDA contains a report which discusses the liver function SAEs from the controlled studies and a report of an integrated analysis of liver safety in Phase 2. See electronic submission at \\CDSESUB1\EVSPROD\NDA022406\022406.enx. A copy of the proposed labeling is attached.

SIGNATURE OF REQUESTER Diane Leaman, RPM	METHOD OF DELIVERY (Check one) X DFS ☐ EMAIL ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Diane V Leaman

9/16/2008 06:12:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: CDERDCRPQT attention: Devi Kozeli

FROM: Diane Leaman, SRPM, Division of Medical Imaging and Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 12, 2008		NNDA 22-406	N	July 28, 2008

NAME OF DRUG	PRIORITY CONSIDERATIONS	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xarelto™ (Rivaroxaban) Tablets	Standard	Anti Xa	March 2, 2009

NAME OF FIRM: Johnson & Johnson

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
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- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review QTC study results. The network location is: \\CDSESUB1\EVSPROD\NDA022406\022406.enx

In addition, the following submission was received on September 24, 2008:

ECG Warehouse Notification		Upload ID:	20080721111244
Sponsor:	Bayer Healthcare Pharmaceuticals	Status:	FDA Access Granted
Study:	NDA 022406 / 11275	Action:	None (Ready For Regulatory Review)

Attention: Cesar Vinces, Cesar Vinces, Leaman, Diane V, FDA Reviewers, and ECG Warehouse Administrators

The study designated as "11275" that is part of FDA application "NDA 022406" has been imported into the ECG

regulatory review. An e-mail with the attachment was sent to Devi Kozeli on September 24, 2008.

Please also reference [redacted] (b) (4) that are being reviewed by DCRP and send a copy of your conslt to Alison Blaus, RPM.

If you have any questions, please reply to this message.

If you have any questions, please call Diane Leaman at 301 796-1424.

SIGNATURE OF REQUESTER Diane Leaman, SRPM	METHOD OF DELIVERY (Check one) X DFS ☐ E-MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Diane V Leaman
9/25/2008 04:49:34 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM (*Name, Office/Division, and Phone Number of Requestor)*:
Division of Cardiovascular and Renal Products: c/o Dr. Norman Stockbridge/Stephen Grant	Diane Leaman/Office of Oncology Drug Products/Division of Medical Imaging and Hematology Products/301-796-1424

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 26, 2008		22-406	NDA	July 22, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xarelto (rivaroxaban) tablets	Std	Anti Xa	

NAME OF FIRM: Johnson and Johnson Pharmaceutical Research & Development, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☒ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: Please provide a general perspective on the major study outcomes for Xarelto. This indicatino is for prophylaxis of deep vein thrombosis and Pulmonary embolism in patients udnergoing hip replacement sruger or knee replacement surgery. See electronic submission at \\CDSESUB1\EVSPROD\NDA022406\022406.enx.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Diane Leaman, RPM	☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Diane V Leaman
8/26/2008 03:01:31 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
CDER OSE CONSULTS

FROM: Diane Leaman/Office of Oncology Drug Products/Division of Medical Imaging and Hematology Products/301-796-1424

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
August 26, 2008		22-406	NDA	July 22, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xarelto (rivaroxaban) tablets	standard	Anti-Xa	

NAME OF FIRM: Johnson and Johnson Pharmaceutical Research & Development, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*: **Trade name review**

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the tradename Xarelto (rivaroxaban) tablets. Please find enclosed the proposed package insert and the proposed immediate container and carton labeling. (Note that the name was submitted to IND 64,892 on August 23, 2007).

PDUFA DATE:
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC: Archival IND/NDA
HFD-160/Division File
HFD-160/RPM
HFD-160/Reviewers and Team Leaders

NAME AND PHONE NUMBER OF REQUESTER	METHOD OF DELIVERY (Check one)
Diane Leaman, 301 796-1424	☒ DFS ONLY ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

5/28/05

36 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

Diane V Leaman
8/26/2008 03:00:56 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-406

NDA ACKNOWLEDGMENT

Johnson and Johnson Pharmaceutical Research and Development LLC
Attention: Andrea F. Kollath
DVM Director, Regulatory Affairs
920 U.S. Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear M. Kollath:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Xarelto™ (Rivaroxaban) Tablets

Date of Application: July 22, 2008

Date of Receipt: July 28, 2008

Our Reference Number: NDA 22-406

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 26, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http:www.fda.gov/cder/ddms/binders.htm.

If you have any questions, call me at (301) 796-1424.

Sincerely,

{See appended electronic signature page}

Diane Leaman
Acting, Safety Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Diane V Leaman
8/5/2008 11:53:17 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: ODS: Ms. Janet Anderson, OSE/Dr. Claudia Karwoski, Mary Willy, Susan Berkman, Jody Duckhorn, Mary Dempsey

FROM: Diane Leaman, SRPM, Division of Medical Imaging and Hematology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
			N	July 28, 2008

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Xarelto™ (Rivaroxaban) Tablets	Standard	Anti-Xa	February 13, 2008

NAME OF FIRM: Johnson and Johnson

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

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- ☐ IN-VIVO WAIVER REQUEST

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- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the sponsor's Safety Surveillance plan (see attached). It is also located in the EDR at: **\CDSESUB1\EVSPROD\NDA022406\0000**

Please also include review of adverse events as related to risk management, particularly with liver injury.

Xarelto is a new oral anticoagulant currently under review for a short term indication for the prophylaxis of VTE in patients undergoing hip or knee replacement surgeries. The proposed maximum treatment duration is 35 days for the short term indication. However, the drug may be used off-label as a long-term treatment to replace Coumadin if it is approved. Clinical trials to support long-term indications are currently ongoing. Current data (short-term) have raised some concerns regarding possible liver injury; the review is continuing. This NDA will be presented and discussed at an Advisory Committee meeting on March 19, 2009. Please evaluate the proposed safety surveillance plan and provide comments and any recommendations for a possible risk management plan for this product.

Also, we would appreciate your designating an OSE reviewer to attend Xarelto Team meetings on an ongoing basis and to prepare a risk management presentation/comments for the March 19, 2009 advisory committee meeting.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Diane Leaman, SRPM, DMIHP	X DFS ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Diane V Leaman

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